Research Article

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# Synthesis of amides and esters containing furan rings under microwave-assisted conditions

https://doi.org/10.1515/chem-2021-0034
received August 25, 2020; accepted February 8, 2021

**Abstract:** In this work, we present a novel method for the synthesis of ester and amide derivatives containing furan rings (furfural derivatives) under mild synthetic conditions supported by microwave radiation. *N*-(Furan-2-ylmethyl)furan-2-carboxamide and furan-2-ylmethyl furan-2-carboxylate were produced using 2-furoic acid, furfurylamine, and furfuryl alcohol. The reactions were carried out in a microwave reactor in the presence of effective coupling reagents: DMT/NMM/$TsO^-$ or EDC. The reaction time, the solvent, and the amounts of the substrates were optimized. After crystallization or flash chromatography, the final compounds were isolated with good or very good yields. Our method allows for the synthesis of *N*-blocked amides using *N*-blocked amino acids (Boc, Cbz, Fmoc) and amine. As well as compounds with a monoamide and ester moiety, products with diamides and diester bonds (*N*,*N*-bis(furan-2-ylmethyl) furan-2,5-dicarboxamide, bis(furan-2-ylmethyl) furan-2,5-dicarboxylate, and furan-3,4-diylbis(methylene) bis(furan-2-carboxylate)) were synthesized with moderate yields in the presence of DMT/NMM/$TsO^-$ or EDC, using 2,5-furandicarboxylic acid and 3,4-bis(hydroxymethyl)furan as substrates.

**Keywords:** microwave chemistry, furfuryl alcohol, furoic acid, amides, coupling reagent

## 1 Introduction

The production of chemicals from biomass offers both economic and ecological benefits, according to the principles of the circular economy. Bioproducts are chemicals that add value to biorefinery processes or materials derived from renewable resources, such as commodity sugars, lignocellulosic biomass, or algae. Ready-to-use bio-compounds (e.g., solvents) or semifinished products used as raw materials in further processes are especially valuable [1–3]. The broad range of uses and wide variety of bio-based products requires individual case studies of each product. Among the many compounds that make up biomass, more than 30 chemicals have been highlighted as having valuable applications [4–7]. These compounds include acetic acid, acetone, acrylonitrile, acrylic acid, adipic acid, benzene, butanediol (1,4-), butadiene (1,3-), epichlorohydrin, ethyl acetate, ethyl lactate, ethylene, fatty acids, fatty alcohols, FDCA, furfural, glycerol, 3-HPA, isoprene, lactic acid, levulinic acid, lipids, oxo chemicals, phenol, propanediol, propylene glycol, sorbitol, succinic acid, THF, xylene (para), PHA, and xylitol.

Furfural is one of the 30 compounds produced by bio-refining biomass [8,9]. Furfural can be transformed by selective hydrogenation, oxidation, hydrogenolysis, and decarboxylation processes [10–14] into a number of C4 and C5 compounds, which are important raw materials for the production of hydrocarbon fuels and fuel additives, as well as for the synthesis of valuable chemicals [15–18]. For the production of biofuels and fuel additives, furfural is most often selectively hydrogenated to form 2-methylfuran (2-MF) and 2-methyltetrahydrofuran (2-MTHF) [19,20]. Furfural can also be used as a substrate for the production of various valuable C4 and C5 chemicals, the most interesting of which are valerolactone, pentanediols, cyclopentanone, dicarboxylic acids, butanediol, and butyrolactone. Most of the C5 chemicals derived from furfural are obtained by selective hydrogenation and/or hydrogenolysis. The C4 chemicals are mainly synthesized by selective oxidation. Valuable

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chemicals derived from furfural thus include fuel components, C5 chemicals, and C4 chemicals [4,21–25].

Furfural and 5-(hydroxymethyl)furfural (HMF) are also raw materials for the preparation of 2,5-furandicarboxylic acid (FDCA) [26–28]. FDCAs are of great interest, due to their similarity to terephthalic acid (PTA), which is a precursor to polyethylene terephthalate (PET) [29,30]. Due to its many excellent properties, PET is the main material used in packaging. However, due to the poor biodegradability of PET, there is great interest in finding new biodegradable polyester materials. Furan-based polymers could meet these requirements and thus reduce the environmental impact of non-renewable packaging materials [31–34]. An additional advantage of FDCA-based polyesters is that renewable biomass can be used to obtain raw materials for their production. Numerous studies have described the production and properties of a series of FDCA-based polyesters: poly(ethylenefuranoate) (PEF) [35–37], poly(propylene furanoate) (PPF) [38], and poly(butylene furanoate) (PBF) [39]. The gas permeability of these polymers exceeds that of PET. It has been reported that 2,2′-bifuran-5,5′-dicarboxylic acid (BFDCA) can be used as a precursor for novel bio-based polyamides and polyesters [40–42]. Derived from furfural, BFDCA is a C10 biheteroaryl monomer useful in the synthesis of new polymers [43–46].

Classic methods of achieving polyamides and polyesters, including those derived from furan derivatives, require extreme conditions (high temperatures, pressures) or the use of sophisticated catalysts [47–51]. Therefore, new, gentler, and more environmentally-friendly methods of obtaining polyamides and polyesters are being sought. Here, we investigate the microwave-assisted synthesis of amide and ester derivatives containing a furan ring. These derivatives could extend the pool of valuable compounds derived from furfural, one of the products of biorefinery transformations. The aim was to produce derivatives derived from furfural containing one functional group (2-furoic acid (**1**), furfurylamine (**2**), furfuryl alcohol (**3**)), as well as disubstituted furan derivatives (2,5-furandicarboxylic acid (**4**), and 3,4-bis(hydroxymethyl)furan (**5**)) (Figure 1). This method would enable the synthesis of peptides using Cbz-, Boc-, and Fmoc-protected substrates as well as unnatural amino acids.

We planned to use these derivatives in the synthesis of compounds with amide and bis-amide moieties, as well as ester and diester moieties containing a furan ring. It was assumed that the selected starting substrates would be obtained directly from furfural, confirming the potential application of this molecule. The extremely mild coupling conditions of microwave-assisted synthesis

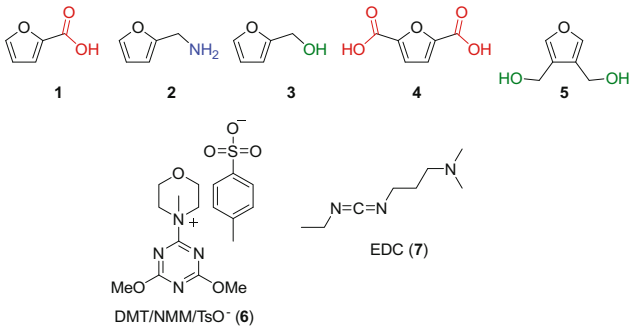



**Figure 1:** Structures of substrates **1–5** and coupling reagents **6–7**.

with condensing reagents would not require high temperatures, long reaction times, and acid catalysts used in classical methods of ester synthesis. As coupling reagents, we selected 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium toluene-4-sulfonate (DMT/NMM/TsO$^-$, **6**) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, **7**). Both DMT/NMM/TsO$^-$ [52,53] and EDC [54–56] are effective, inexpensive, and environmentally friendly coupling reagents for the synthesis of amides, esters, and peptides both in solution and in solid phases.

# 2 Experimental

## 2.1 Materials and methods

NMR spectra were measured on a Bruker Avance DPX spectrometer (250.13 MHz for $^1$H NMR) and Bruker Avance II Plus spectrometer (700 MHz for $^1$H NMR and 176 MHz for $^{13}$C NMR) in $CDCl_3$ solution. $^1$H and $^{13}$C NMR spectra were referenced according to the residual peak of the solvent, based on literature data. The chemical shift ($\delta$) was reported in ppm and coupling constant ($J$) in Hz. $^{13}$C NMR spectra were proton-decoupled. A monomode microwave reactor (CEM Discover) equipped with an IntelliVent pressure control system was used. The standard method was applied, and the maximum pressure was set to 250 psi. The temperatures of the reaction mixtures were measured with an external infrared sensor. Flash chromatography was performed in a glass column packed with Baker silica gel (30–60 µm). For TLC, silica gel was used on TLC Al foils (Sigma-Aldrich) with an indicator of 254 nm. All reagents and solvents were purchased from Sigma-Aldrich (Poland) and used as obtained. GC-MS spectra were measured on a GC-Perkin Elmer Clarus 580, MS-Perkin Elmer Clarus SQ8S. Melting

points were determined using a Büchi SMP-20 apparatus. Mass spectrometry analysis was performed on a Bruker microOTOF-QIII (Bruker Corporation, Billerica, MA, USA) supplied with electrospray ionization mode and time of flight detector (TOF). IR spectra were measured on an FT-IR Alpha Bruker (ATR) instrument and were reported in $cm^{-1}$. The furfuryl alcohol and 3,4-bis(hydroxymethyl) furan were commercially available (Sigma-Aldrich).

## 2.2 General procedure for the synthesis of amides 15, 17a–b, and 18

In a 10 mL pressure vial equipped with a magnetic bar, acid **1**, **13,** or **16a**–**b** (2.6 mmol, 1.3 equiv.), DMT/NMM/TsO$^-$ (**6**) (1.076 g, 2.6 mmol, 1.3 equiv.), and NMM (0.09 mL, 0.78 mmol, 0.3 equiv.) were dissolved in DCM (3 mL). Next, amine **2** or **14** (2 mmol 1 equiv.) was added dropwise, and the reaction was performed under MW conditions (standard mode, 10 min, 90°C). After this time, the reaction mixture was diluted with DCM (50 mL), washed successively using $H_2O$ (5 mL), 1 N HCl (2 × 5 mL), $H_2O$ (5 mL), 1 M NaOH (2 × 5 mL), and $H_2O$ (5 mL), and then dried under anhydrous $MgSO_4$. The crude products were purified by crystallization (ethyl acetate/hexane).

### 2.2.1 *N*-Benzyl-*p*-chlorobenzamide (15)

White solid, mp 163–164°C (lit. 161–163°C). Yield 88% (0.433 g). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.72 (d, $J_{HH}$ = 8.7 Hz, 2H, C$H_{Ar}$), 7.39 (d, $J_{HH}$ = 8.7 Hz, 2H, C$H_{Ar}$), 7.36–7.30 (m, 5H, C$H_{Ar}$), 6.46 (bs, 1H, N*H*), 4.62 (d, $J_{HH}$ = 5.7 Hz, 2H, C$H_2$). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 166.4 (1C, *C*O), 138.1 (1C, $C_{Ar}$), 137.9 (1C, $C_{Ar}$), 132.8 (1C, $C_{Ar}$), 128.9 (4C, 4 × $C_{Ar}$H), 128.5 (2C, 2 × $C_{Ar}$H), 128.1 (2C, 2 × $C_{Ar}$H), 127.8 (1C, $C_{Ar}$H), 44.3 (1C, *C*H$_2$). IR (ATR): 1,638 (CO), 1,592, 1,550, 1,482, 710 (Ar), 668 (Ar) $cm^{-1}$. HRMS: 244.9791, ([M]$^+$, $C_{14}H_{12}ClNO^+$; calc. 245.0607). The analytical data are in agreement with those reported previously in the literature [57].

### 2.2.2 (*S*)-*N*-Boc-phenylalanine benzylamide (17a)

White solid, mp 132–133°C (lit. 134°C). Yield 83% (0.585 g). $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.30–7.11 (m, 10H, C$H_{Ar}$), 6.26 (bs, 1H, N*H*), 5.16 (bs, 1H, N*H*), 4.40–4.33 (m, 3H, PhC$H_2$C*H*), 3.13–3.07 (m, 2H, C$H_2$Ph), 1.41 (s, 9H, 3 × (C*H*)$_3$). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 171.2, 155.8, 137.8, 136.8, 129.4, 128.8, 128.7, 127.7, 127.5, 127.0, 80.3, 56.1, 43.5, 38.7, 28.3. IR (ATR): 1,657 (CO), 1,521 (CO), 1,294 (NH), 1,233 (NH), 1,169 (NH), 694 (Ar) $cm^{-1}$. HRMS: 354.1907, ([M]$^+$, $C_{21}H_{26}N_2O_3^+$; calc. 354.1943). The analytical data are in agreement with those reported previously in the literature [58].

### 2.2.3 (*S*)-*N*-Cbz-phenylalanine benzylamide (17b)

White solid, mp 140–141°C (lit. 142–144°C). Yield 88% (0.679 g). $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.37–7.34 (m, 3H, C$H_{Ar}$), 7.31–7.24 (m, 8H, C$H_{Ar}$), 7.19–7.18 (m, 2H, C$H_{Ar}$), 7.09–7.08 (m, 2H, C$H_{Ar}$), 6.24 (bs, 1H, N*H*), 5.52 (bs, 1H, N*H*), 5.06–5.01 (m, 2H, OC$H_2$Ph), 4.49–4.48 (bs, 1H, C*H*), 4.39–4.30 (m, 2H, PhC$H_2$CH), 3.16–3.06 (m, 2H, NHC$H_2$Ph). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 170.8, 156.1, 137.6, 136.5, 136.2, 129.4, 128.8, 128.7, 128.6, 128.3, 128.1, 127.8, 127.6, 127.1, 67.1, 56.5, 43.6, 38.9. IR (ATR): 1,685, 1,644 (CO), 1,529, 1,236 (NH), 741 (Ar), 694 (Ar) $cm^{-1}$. HRMS: 389.1815, ([M + H]$^+$, $C_{24}H_{25}N_2O_3^+$; calc. 389.1860). The analytical data are in agreement with those reported previously in the literature [59].

### 2.2.4 *N*-(Furan-2-ylmethyl)furan-2-carboxamide (18)

White solid, 79–80°C. Yield 84% (0.32 g). $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.41 (dd, $J_{HH}$ = 1.7 Hz, $J_{HH}$ = 0.8 Hz, 1H, C$H_{Ar}$), 7.35 (dd, $J_{HH}$ = 1.8 Hz, $J_{HH}$ = 0.8 Hz, 1H, C$H_{Ar}$), 7.12 (dd, $J_{HH}$ = 3.5 Hz, $J_{HH}$ = 0.8 Hz, 1H, C$H_{Ar}$), 6.7 (bs, 1H, N*H*), 6.47 (dd, $J_{HH}$ = 3.5 Hz, $J_{HH}$ = 1.8 Hz, 1H, C$H_{Ar}$), 6.32 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 1.9 Hz, 1H, C$H_{Ar}$), 6.27 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 0.7 Hz, 1H, C$H_{Ar}$), 4.59 (d, $J_{HH}$ = 5.7 Hz, 2H, C$H_2$). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 158.1 (1C, *C*O), 151.1 (1C, O$C_{Ar}$), 147.8 (1C, O$C_{Ar}$), 144.0 (1C, OC$_{Ar}$H), 142.4 (1C, OC$_{Ar}$H), 114.5 (1C, $C_{Ar}$H), 112.2 (1C, $C_{Ar}$H), 110.5 (1C, $C_{Ar}$H), 107.7 (1C, $C_{Ar}$H), 36.1 (1C, *C*H$_2$). IR (ATR): 1,700 (CO), 1,642 (CO), 1,590, 1,239 (NH), 1,007, 746 (Ar), 699 (Ar) $cm^{-1}$. HRMS: 191.0380, ([M$^+$, $C_{10}H_9NO_3^+$; calc. 191.0582). New compound.

## 2.3 Procedure for the synthesis of (*S*)-*N*-Fmoc-phenylalanine benzylamide (17c)

In a 10-mL pressure vial equipped with a magnetic bar, *N*-Fmoc-phenylalanine **16c** (0.503 g, 1.3 mmol, 1.3 equiv.), DMT/NMM/TsO$^-$ (**6**) (0.538 g, 1.3 mmol, 1.3 equiv.), and

NMM (0.45 mL, 0.39 mmol, 0.3 equiv.) were dissolved in DCM (3 mL). Next, benzylamine (**14**) (1 mmol 1 equiv.) was added dropwise, and the reaction was carried under MW conditions (standard mode, 40 min, 90°C). Next, the reaction mixture was diluted with DCM (30 mL) washed successively using $H_2O$ (3 mL), 1 N HCl (2 × 3 mL), $H_2O$ (3 mL), 1 M NaOH (2 × 3 mL), and $H_2O$ (3 mL), and dried under anhydrous $MgSO_4$. The crude products were purified by crystallization (ethyl acetate/hexane). White solid, mp 193–195°C. Yield 73% (0.347 g). $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.76 (d, $J_{HH}$ = 7.1 Hz, 2H, C$H_{Ar}$), 7.53 (t, $J_{HH}$ = 7.1 Hz, 2H, C$H_{Ar}$), 7.40 (t, $J_{HH}$ = 7.1 Hz, 2H, C$H_{Ar}$), 7.32–7.24 (m, 8H, C$H_{Ar}$), 7.17 (bs, 2H, C$H_{Ar}$), 7.06 (bs, 2H, C$H_{Ar}$), 5.93 (bs, 1H, N$H$), 5.39 (bs, 1H, N$H$), 4.41–4.34 (m, 5H, C$H_2$C$H$, OC$H_2$), 4.17 (t, $J_{HH}$ = 6.8 Hz, 1H, C$H$), 3.14–3.05 (m, 2H, NHC$H_2$Ph). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 170.6, 143.8, 141.4, 137.6, 129.4, 128.9, 128.7, 127.9, 127.8, 127.7, 127.2, 125.1, 120.1, 67.1, 56.6, 47.3, 43.7, 38.9. IR (ATR): 1,686, 1,651 (CO), 1,531, 1,258 (NH), 1,231 (NH), 738 (Ar), 697 (Ar) cm$^{-1}$. HRMS: 476.2089, ([M]$^+$, $C_{31}H_{28}N_2O_3^+$; calc. 476.2100). New compound.

## 2.4 Procedure for the synthesis of furan-2-ylmethyl furan-2-carboxylate (19) using DMT/NMM/TsO$^-$

2-Furoic acid (**1**) (0.291 g, 2.6 mmol, 1.3 equiv.), DMT/NMM/TsO$^-$ (**6**) (1.076 g, 2.6 mmol, 1.3 equiv.), and NMM (0.09 mL, 0.78 mmol, 0.3 equiv.) were dissolved in DCM (3 mL) using a 10-mL pressure vial. Next, furfuryl alcohol (**3**) (0.17 mL, 2 mmol, 1 equiv.) was added and the reaction was carried out under MW conditions (standard mode, 30 min, 90°C). The reaction mixture was then diluted with DCM (50 mL), washed successively using $H_2O$ (5 mL), 1 N HCl (2 × 5 mL), $H_2O$ (5 mL), 1 M NaOH (2 × 5 mL), $H_2O$ (5 mL), and dried under anhydrous $MgSO_4$. Product **19** was purified by flash chromatography (hexane/ethyl acetate 10:1) and obtained as yellow oil with 49% yield (0.188 g).

## 2.5 Procedure for the synthesis of furan-2-ylmethyl furan-2-carboxylate (19) using EDC

2-Furoic acid (**1**) (0.672 g, 6 mmol, 3 equiv.) and EDC (**7**) (1.06 mL, 6 mmol, 3 equiv.) were dissolved in DCM (3 mL) using a 10-mL pressure vial. Next, furfuryl alcohol (**3**) (0.17 mL, 2 mmol, 1 equiv.) was added, and the reaction was carried out under MW conditions (standard mode, 30 min, 90°C). The reaction mixture was then diluted with DCM (50 mL), washed successively using $H_2O$ (5 mL), 1 N HCl (2 × 5 mL), $H_2O$ (5 mL), 1 M NaOH (2 × 5 mL), and $H_2O$ (5 mL), and dried under anhydrous $MgSO_4$. Product **19** was purified by flash chromatography (hexane/ethyl acetate 10:1) and obtained as yellow oil with 71% yield (0.272 g). $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.56 (dd, $J_{HH}$ = 1.7 Hz, $J_{HH}$ = 0.9 Hz, 1H, C$H_{Ar}$), 7.43 (dd, $J_{HH}$ = 1.8 Hz, $J_{HH}$ = 0.8 Hz, 1H, C$H_{Ar}$), 7.19 (dd, $J_{HH}$ = 3.5 Hz, $J_{HH}$ = 0.8 Hz, 1H, C$H_{Ar}$), 6.49–6.48 (m, 2H, 2 × C$H_{Ar}$), 6.37 (dd, $J_{HH}$ = 3.3 Hz, $J_{HH}$ = 1.8 Hz, 1H, C$H_{Ar}$), 5.28 (s, 2H, C$H_2$). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 158.4 (1C, $C$O), 149.2 (1C, $C_{Ar}$O), 146.6 (1C, $C_{Ar}$H), 144.4 (1C, $C_{Ar}$O), 143.5 (1C, $C_{Ar}$H), 118.5 (1C, $C_{Ar}$H), 111.9 (1C, $C_{Ar}$H), 111.2 (1C, $C_{Ar}$H), 110.7 (1C, $C_{Ar}$H), 58.4 (1C, $C$H$_2$). IR (ATR): 1,712 (CO), 1,289, 1,171, 1,104, 744 (Ar) cm$^{-1}$. HRMS: 192.0460, ([M]$^+$, $C_{10}H_8O_4^+$; calc. 192.0423). The analytical data are in agreement with those reported previously in the literature [60].

## 2.6 Procedure for the synthesis of *N*,*N*-bis(furan-2-ylmethyl)furan-2,5-dicarboxamide (20)

2,5-Furandicarboxylic acid (**4**) (0.468 g, 3 mmol, 1.5 equiv.), DMT/NMM/TsO$^-$ (**6**) (1.242 g, 3 mmol, 1.5 equiv.), and NMM (0.1 mL, 0.9 mmol, 0.3 equiv.) were dissolved in DCM (3 mL) in a 10-mL pressure vial. After that, furfurylamine (**2**) (0.18 mL, 2 mmol, 1 equiv.) was added dropwise, and the reaction was carried out under MW conditions (standard mode, 30 min, 90°C). The reaction mixture was then diluted with DCM (50 mL), washed successively using $H_2O$ (5 mL), 1 N HCl (2 × 5 mL), $H_2O$ (5 mL), 1 M NaOH (2 × 5 mL), and $H_2O$ (5 mL), and dried under anhydrous $MgSO_4$. The product was isolated after crystallization (ethyl acetate/hexane) with a yield of 37% (0.233 g). White solid, mp 163–164°C. $^1$H NMR (700 MHz, DMSO-d$_6$): $\delta$ 8.95 (t, $J_{HH}$ = 5.9 Hz, 2H, 2 × N$H$), 7.60 (dd, $J_{HH}$ = 1.8 Hz, $J_{HH}$ = 0.9 Hz, 2H, 2 × C$H_{Ar}$), 7.18 (s, 2H, 2 × C$H_{Ar}$), 6.41 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 1.9 Hz, 2H, 2 × C$H_{Ar}$), 6.32 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 0.8 Hz, 2H, 2 × C$H_{Ar}$), 4.49 (d, $J_{HH}$ = 5.9 Hz, 4 H 2 × C$H_2$). $^{13}$C NMR (176 MHz, DMSO-d$_6$): $\delta$ 157.4 (2C, 2 × $C$O), 152.1 (2C, 2 × $C_{Ar}$O), 148.3 (2C, 2 × $C_{Ar}$O), 142.8 (2C, 2 × $C_{Ar}$H), 115.3 (2C, 2 × $C_{Ar}$H), 111.0 (2C, 2 × $C_{Ar}$H), 107.8 (2C, 2 × $C_{Ar}$H), 35.6 (2C, 2 × $C$H$_2$). IR (ATR): 1,732 (CO), 1,596, 1,570, 1,279, 738 cm$^{-1}$. HRMS: 315.0944, ([M + H]$^+$, $C_{16}H_{15}N_2O_5^+$; calc. 315.0975). New compound.

#### 2.6.1 *N*-(Furan-2-ylmethyl)-4,6-dimethoxy-1,3,5-triazin-2-amine (21)

Yield 23%. White solid, mp 105–106°C. $^1$H NMR (700 MHz, DMSO-$d_6$): $\delta$ 8.33 (t, $J_{HH}$ = 6.0 Hz, 1H, N*H*), 7.55 (dd, $J_{HH}$ = 1.8 Hz, $J_{HH}$ = 0.8 Hz, 1H, C$H_{Ar}$), 6.37 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 1.8 Hz, 1H, C$H_{Ar}$), 6.25 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 0.8 Hz, 1H, C$H_{Ar}$), 4.47 (d, $J_{HH}$ = 6.0 Hz, 2H, C$H_2$), 3.84 (s, 3H, C$H_3$), 3.81 (s, 3H, C$H_3$). $^{13}$C NMR (176 MHz, DMSO-$d_6$): $\delta$ 172.4 (1C, $C_{Ar}$OMe), 172.2 (1C, $C_{Ar}$OMe), 168.1 (1C, $C_{Ar}$NH), 152.6 (1C, $C_{Ar}$O), 142.4 (1C, $C_{Ar}$H), 110.9 (1C, $C_{Ar}$H), 107.4 (1C, $C_{Ar}$H), 54.6 (1C, $C$H$_3$O), 54.6 (1C, $C$H$_3$O), 37.6 (1C, $C$H$_2$). IR (ATR): 1,619, 1,570, 1,459, 1,360, 1,341, 1,105, 1,071, 1,049, 812 cm$^{-1}$. HRMS: 236.1292, ([M]$^+$, $C_{10}H_{12}N_4O_3^+$; calc. 236.0909). New compound.

## 2.7 Procedure for the synthesis of bis(furan-2-ylmethyl) furan-2,5-dicarboxylate (22)

In a 10-mL pressure vial, 2,5-furandicarboxylic acid (**4**) (0.468 g, 3 mmol, 1.5 equiv.) and EDC (**7**) (1.06 mL, 6 mmol, 3 equiv.) were dissolved in DCM (3 mL). Furfuryl alcohol (**3**) (0.17 mL, 2 mmol, 1 equiv.) was then added. The reaction was carried out under MW conditions (standard mode, 30 min, 90°C). The reaction mixture was then diluted with DCM (50 mL), washed successively using $H_2O$ (5 mL), 1 N HCl (2 × 5 mL), $H_2O$ (5 mL), 1 M NaOH (2 × 5 mL), and $H_2O$ (5 mL), and dried under anhydrous $MgSO_4$. The product was isolated as a yellow oil after flash chromatography (hexane: ethyl acetate 3:1) with a of yield 7% (0.04 g). $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.43 (dd, $J_{HH}$ = 1.9 Hz, $J_{HH}$ = 0.8 Hz, 2H, 2 × C$H_{Ar}$), 7.20 (s, 2H, 2 × C$H_{Ar}$), 6.48 (dd, $J_{HH}$ = 3.3 Hz, $J_{HH}$ = 0.6 Hz, 2H, 2 × C$H_{Ar}$), 6.36 (dd, $J_{HH}$ = 3.3 Hz, $J_{HH}$ = 1.8 Hz, 2H, 2 × C$H_{Ar}$), 5.30 (s, 4H, 2 × C$H_2$). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 157.3 (2C, 2 × *C*O), 148.6 (2C, 2 × $C_{Ar}$O), 146.2 (2C, 2 × $C_{Ar}$O), 143.4 (2C, 2 × $C_{Ar}$H), 118.7 (2C, 2 × $C_{Ar}$H), 111.4 (2C, 2 × $C_{Ar}$H), 110.6 (2C, 2 × $C_{Ar}$H), 58.6 (2C, 2 × $C$H$_2$). HRMS: 317.0658; ([M + H]$^+$, $C_{16}H_{13}O_7^+$; calc. 317.0656). New compound.

## 2.8 Procedure for the synthesis of furan-3,4-diylbis(methylene) bis(furan-2-carboxylate) (23)

In a 10-mL pressure vial, 2-furoic acid (**1**) (0.224 g, 2 mmol, 2 equiv.) and EDC (**7**) (0.35 mL, 2 mmol, 2 equiv.) were dissolved in DCM (3 mL), to which 3,4-bis (hydroxymethyl)furan (**5**) (0.1 mL, 1 mmol, 1 equiv.) was then added. The reaction was carried out under MW conditions (standard mode, 30 min, 90°C). The reaction mixture was next diluted with DCM (50 mL), washed successively using $H_2O$ (5 mL), 1 N HCl (2 × 5 mL), $H_2O$ (5 mL), 1 M NaOH (2 × 5 mL), and $H_2O$ (5 mL), and dried under anhydrous $MgSO_4$. The product was isolated as a yellow oil after flash chromatography (hexane:ethyl acetate 5:1) and PTLC (hexane:acetone 3:1) with 9% (0.09 g) of yield. $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.55 (s, 2H, 2 × C$H_{Ar}$), 7.53 (s, 2H, 2 × C$H_{Ar}$), 7.14 (d, $J_{HH}$ = 3.5 Hz, 2H, 2 × C$H_{Ar}$), 6.46 (dd, $J_{HH}$ = 3.5 Hz, $J_{HH}$ = 1.7 Hz, 2H, 2 × C$H_{Ar}$), 5.29 (s, 4H, 2 × C$H_2$). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 158.5 (2C, 2 × *C*O), 146.5 (2C, 2 × $C_{Ar}$H), 144.5 (2C, 2 × $C_{Ar}$O), 143.2 (2C, 2 × $C_{Ar}$H), 119.8 (2C, 2 × $C_{Ar}$), 118.3 (2C, 2 × $C_{Ar}$H), 111.9 (2C, 2 × $C_{Ar}$H), 56.8 (2C, 2 × $C$H$_2$). IR (ATR): 1,729 (CO), 1,706 (CO), 1,469, 1,306, 1,181, 1,112, 760 (Ar) cm$^{-1}$. HRMS: 317.0659; ([M + H]$^+$, $C_{16}H_{13}O_7^+$; calc. 317.0656). New compound.

#### 2.8.1 (4-(Hydroxymethyl)furan-3-yl)methyl furan-2-carboxylate (24)

Yield (35%), white solid, mp 89–90°C. $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.56 (s, 1H, C$H_{Ar}$), 7.51 (s, 1H, C$H_{Ar}$), 7.42 (s, 1H, C$H_{Ar}$), 7.20 (d, $J_{HH}$ = 3.5 Hz, 1H, C$H_{Ar}$), 6.50 (dd, $J_{HH}$ = 3.5 Hz, $J_{HH}$ = 1.7 Hz, 1H, C$H_{Ar}$), 5.28 (s, 2H, C$H_2$), 4.60 (s, 2H, C$H_2$OH), 2.28 (bs, 1H, O*H*). $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 158.5 (1C, *C*O), 146.6 (1C, $C_{Ar}$H), 144.4 (1C, $C_{Ar}$O), 143.2 (1C, $C_{Ar}$H), 141.5 (1C, $C_{Ar}$H), 124.7 (1C, $C_{Ar}$H), 119.4 (1C, $C_{Ar}$H), 118.6 (1C, $C_{Ar}$H), 112.1 (1C, $C_{Ar}$H), 57.2 (1C, $C$H$_2$), 55.2 (1C, $C$H$_2$). IR (ATR): 1,720 (CO), 1,564, 1,295, 1,178, 1,112, 1,013, 823, 729 (Ar) cm$^{-1}$. HRMS: 222.0760, ([M]$^+$, $C_{11}H_{10}O_5^+$; calc. 222.0528). New compound.

## 2.9 Synthesis of furoic acid (1)

#### 2.9.1 Synthesis of furoic acid (1) using $H_2O_2$ and CuCl as a catalyst

Freshly distilled furfural (4.15 mL, 50 mmol), CuCl (0.247 g, 2.5 mmol), and acetonitrile (100 mL) were placed in a 250-mL round-bottom flask, and 30% $H_2O_2$ (10.2 mL, 100 mmol) was slowly added to the mixture dropwise for 30 min. The reaction was carried out at room temperature. An additional portion of 30% $H_2O_2$ (2.55 mL, 25 mmol) was added after 2 h. After 4 h, the substrate was found to be present, so another portion of 30% $H_2O_2$ (2.55 mL, 25 mmol) was added. Stirring was

continued for 20 h at room temperature. The solvent was then removed under reduced pressure, and $H_2O$ (40 mL) and saturated $NaHCO_3$ solution were added to the residue to obtain pH 8.5. The aqueous phase was extracted with ethyl acetate (2 × 30 mL). The aqueous layer was acidified to pH 2 with 2 N HCl, then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. The solvent was evaporated under reduced pressure to give 1.87 g (38%) of the product as a yellow solid. The structure of the obtained product was confirmed based on NMR analysis of the crude product.

Yellow solid, mp 129–130 °C (lit. [61] 130–132°C). $^1$H NMR ($CDCl_3$, 700 MHz): $\delta$ 12.0 (bs, 1H, O*H*), 7.64 (s, 1H, C*H*$_{Ar}$), 7.33 (d, 1H, $J_{HH}$ = 3.4 Hz, C*H*$_{Ar}$), 6.55 (dd, 1H, $J_{HH}$ = 3.4 Hz, $J_{HH}$ = 1.6 Hz, C*H*$_{Ar}$). $^{13}$C NMR ($CDCl_3$, 176 MHz): $\delta$ 163.9 (1C, *C*O), 147.5 (1C, *C*$_{Ar}$H), 143.9 (1C, *C*$_{Ar}$), 120.3 (1C, *C*$_{Ar}$H), 112.4 (1C, *C*$_{Ar}$H). HRMS: 112.0181 ([M]$^+$, $C_5H_4O_3^+$; calc. 112.0160.

The analytical data are in agreement with those reported previously in the literature [61].

### 2.9.2 Synthesis of furoic acid (1) using *t*-BuOOH and $CuBr_2$ as a catalyst

Freshly distilled furfural (0.83 mL 10 mmol), $CuBr_2$ (111.6 mg, 0.5 mmol), and acetonitrile (20 mL) were placed in a 100-mL round-bottom flask equipped with a septum. The reaction was carried out under nitrogen at room temperature. To the mixture, 70% *t*-BuOOH in $H_2O$ (1.3 mL, 10 mmol) was added dropwise for 10 min. The progress of the reaction was monitored by TLC. After 30 min, the solvent was evaporated under reduced pressure, and the residue was dissolved in a saturated $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL). The aqueous phase was acidified to pH 2 using 1 M $NaHSO_4$. The acidified solution was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$. The crude product was crystallized from ethyl acetate–hexane. A yellow product was obtained with a yield of 0.43 g (38%).

Yellow solid, mp 129–130°C (lit. [61] 130–132 °C). $^1$H NMR ($CDCl_3$, 700 MHz): $\delta$ 12.0 (bs, 1H, O*H*), 7.64 (s, 1H, C*H*$_{Ar}$), 7.33 (d, 1H, $J_{HH}$ = 3.4 Hz, C*H*$_{Ar}$), 6.55 (dd, 1H, $J_{HH}$ = 3.4 Hz, $J_{HH}$ = 1.6 Hz, C*H*$_{Ar}$). $^{13}$C NMR ($CDCl_3$, 176 MHz): $\delta$ 163.9 (1C, *C*O), 147.5 (1C, *C*$_{Ar}$H), 143.9 (1C, *C*$_{Ar}$), 120.3 (1C, *C*$_{Ar}$H), 112.4 (1C, *C*$_{Ar}$H). HRMS: 112.0181 ([M]$^+$, $C_5H_4O_3^+$; calc. 112.0160.

The analytical data are in agreement with those reported previously in the literature [61].

## 2.10 Synthesis of furfurylamine (2)

### 2.10.1 Synthesis according to the original procedure

Furfural (5 mL, 60 mmol), $NH_2OH$ (5.04 g, 72.4 mmol), and $H_2O$ (10 mL) were placed in a 250-mL three-necked flask. To the mixture, 15 mL of 2.4 M $Na_2CO_3$ solution was added, and the solution was heated to 60°C. Next, $H_2O$ (16.5 mL), zinc dust (27.6 g, 422.5 mmol), $NH_4Cl$ (16.1 g, 309 mmol), and $ZnCl_2$ (0.82 g, 6.0 mmol) were added. Stirring was continued for 15 min. All insoluble compounds were filtered off under reduced pressure, and 6 M NaOH (100 mL) solution was added to the filtrate. The aqueous phase was extracted using *n*-heptane (3 × 200 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and the solvent was evaporated under reduced pressure. Furfurylamine (**2**) (0.92 g, 16%) was obtained as a light yellow liquid.

$^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.27 (dd, $J_{HH}$ = 1.8 Hz, $J_{HH}$ = 0.9 Hz, 1H, C*H*$_{Ar}$), 6.23 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 1.8 Hz, 1H, C*H*$_{Ar}$), 6.05 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 0.8 Hz, 1H, C*H*$_{Ar}$), 3.73 (s, 2H, C*H*$_2$), 1.35 (bs, 2H, N*H*$_2$). $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 156.7 (1C, *C*$_{Ar}$H), 141.4 (1C, *C*$_{Ar}$), 110.0 (1C, *C*$_{Ar}$H), 104.8 (1C, *C*$_{Ar}$H), 39.2 (1C, *C*H$_2$). HRMS: 98.0452 ([M + H]$^+$, $C_5H_8NO^+$; calc. 98.0600.

The analytical data are in agreement with those reported previously in the literature [62].

### 2.10.2 Optimization experiment I

The reaction was performed according to the general procedure with the following changes: time of the second step of the reaction, 20 min; extraction solvent, MTBE. Product: furfurylamine (**2**), 3.66 g (63%). The product was spectroscopically identical to that described earlier.

### 2.10.3 Optimization experiment II

The reaction was performed according to the general procedure with the following changes: time of the second step of the reaction, 30 min; extraction solvent, MTBE. Product: furfurylamine (**2**), 4.40 g (76%). The product was spectroscopically identical to that described earlier.

### 2.10.4 Optimization experiment III

The reaction was performed according to the general procedure with the following changes: time of the second

step of the reaction, 60 min; extraction solvent, MTBE. Product: furfurylamine (**2**), 4.40 g (76%). The product was spectroscopically identical to that described earlier.

## 2.11 Synthesis of 2,5-furandicarboxylic acid (4)

### 2.11.1 Synthesis of 2-(2-furanyl)-1,3-dioxolane (11) – general procedure

Catalytic amounts of Dowex® cationic ion exchange resin, furfural (8.3 mL, 100 mmol), ethylene glycol (6.15 mL, 110 mmol), and solvent (50 mL) were placed in a 100-mL round-bottom flask equipped with an azeotropic distillation adapter and reflux condenser. The reaction was carried out at the reflux temperature of the solvent. After the evolution of water, the catalyst was filtered off, and then the organic phase was washed with water (2 × 70 mL) and dried over anhydrous $K_2CO_3$. After evaporation of the solvent, the crude product was distilled under reduced pressure.

### 2.11.2 Optimization experiment I

The reaction was carried out according to the general procedure using toluene as the solvent. Reaction time: 4 h. 2-(2-furanyl)-1,3-dioxolane was obtained with a yield of 62% (8.68 g). The structure of the expected product **11** was confirmed based on analysis of NMR and GC-MS spectra.

$^1$H NMR (700 MHz, $CDCl_3$) $\delta$: 4.00 (ddd, 2H, $J^1$ = 6.2 Hz, $J^2$ = 4.0 Hz, $J^3$ = 6.5 Hz), 4.13 (ddd, 2H, $J^1$ = 6.2, Hz, $J^2$ = 4.0 Hz, $J^3$ = 6.0 Hz), 5.93 (s, 1H), 6.36 (dd, 1H, $J^1$ = 3.3 Hz, $J^2$ = 1.8 Hz), 6.45 (dd, 1H, $J^1$ = 3.3 Hz, $J^2$ = 0.8 Hz,), 7.43 (dd, 1H, J = 1.8 Hz, $J^2$ = 0.8 Hz). $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 65.1, 97.7, 108.7, 110.1, 143.12, 151.1. *m/z*: 140.076.

The analytical data are in agreement with those reported previously in the literature [63].

### 2.11.3 Optimization experiment II

The reaction was carried out according to the general procedure using toluene as the solvent. Reaction time: 8 h. Product: 10.08 g (72%). The product was spectroscopically identical to that described above.

### 2.11.4 Optimization experiment III

The reaction was carried out according to the general procedure using 1,2-dichloroethane as the solvent. Reaction time: 6 h. Product: 9.94 g (71%). The product was spectroscopically identical to that described earlier.

### 2.11.5 Optimization experiment IV

The reaction was carried out according to the general procedure using 1,2-dichloroethane as the solvent. Reaction time: 8 h. Product: 11.48 g (82%). The product was spectroscopically identical to that described earlier.

### 2.11.6 Synthesis of 2-(5-formyl-2-furanyl)-1,3-dioxolane (12)

Diisopropylamine (11.25 mL, 80 mmol) was placed in a 500-mL three-necked flask and cooled to –20°C. Then, 2.5 M butyllithium in hexane was added (30 mL, 75 mmol) keeping the temperature at –20°C, and stirring was continued for 15 min. Next, THF (60 mL) was added, and the solution was cooled to –80°C. In the next step, a solution of 2-(2-furanyl)-1,3-dioxolane (7.51 g, 53.6 mmol) in THF (25 mL) was added, and stirring was continued for 30 min while the temperature was maintained at –80°C. After this time, DMF (50 mL) was added, and stirring was continued for 14 h, allowing it to rise slowly to room temperature. Diethyl ether (200 mL) was added to the mixture, and the solution was washed with water (4 × 150 mL). The aqueous layers were extracted again with diethyl ether (2 × 200 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, and the solvent was evaporated off under reduced pressure to give 4.33 g (48%) of the expected product.

$^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 4.09–3.97 (m, 4 H), 5.92 (s, 1 H), 6.55 (d, 1H, $J$ = 3.6 Hz), 7.13 (d, 1H, $J$ = 3.6 Hz), 9.60 (s, 1H). $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 65.4, 97.26, 110.6, 119.15, 152.9, 157.27, 178.1.

The analytical data are in agreement with those reported previously in the literature [63].

### 2.11.7 Synthesis of furan-2,5-dicarboxaldehyde (9)

2-(5-Formyl-2-furanyl)-1,3-dioxolane (0.84 g, 5 mmol), acetone (150 mL), and 6 N HCl (10 mL) were placed in

a 250-mL round-bottom flask. The solution was heated to reflux for 1 h. The solvent was evaporated under reduced pressure, and $CH_2Cl_2$ (150 mL) was added to the residue. The organic phase was washed with 15% $K_2CO_3$ (3 × 100 mL) and $H_2O$ (100 mL) and dried over $Na_2CO_3$. The solvent was removed under reduced pressure. The crude product was crystallized from a mixture of diethyl ether and *n*-heptane. Furan-2,5-dicarboxaldehyde (**9**) was obtained with 95% (0.59 g) of yield.

$^1$H NMR (750 MHz, $CDCl_3$) $\delta$ 7.35 (s, 2H), 9.79 (s, 2H). $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 119.2, 154.3, 179.2.

The analytical data are in agreement with those reported previously in the literature [63].

#### 2.11.8 Synthesis of 2,5-furandicarboxylic acid (4)

Synthesis was carried out according to the procedure for the preparation of furoic acid (**1**), using *t*-BuOOH and $CuBr_2$ as catalyst. Starting materials: furan-2,5-dicarboxaldehyde (**9**) (1.241 g, 10 mmol), $CuBr_2$ (111.6 mg, 0.5 mmol), 70% *t*-BuOOH in $H_2O$ (3.2 mL, 25 mmol). Product: 2,5-furandicarboxylic acid (**4**), 0.812 g (52%), mp = 341–343°C, lit. mp = 340–345°C [65]. $^1$H NMR (700 MHz, DMSO-$d_6$): $\delta$ 13.52 (bs, 2H, *OH*), 7.28 (s, 2H, C*H*$_{Ar}$). $^{13}$C NMR (176 MHz, DMSO-$d_6$): $\delta$ 159,3, 147.5, 118.8. HRMS: 156.0055 ([M]$^+$, $C_6H_4O_5^+$; calc. 156.0056.

The analytical data are in agreement with those reported previously in the literature [64].

**Ethical approval:** The conducted research is not related to either human or animal use.

## 3 Result and discussion

In the first stage of the research, furfural was used to obtain selected furfural derivatives: furoic acid (**1**), furfurylamine (**2**), and 2,5-furandicarboxylic acid (**4**). The syntheses of these compounds were made based on known methods, changing the key parameters so that the developed methods were easier to use on a larger scale (parameters more friendly to production on an industrial scale). In all cases, the raw material was furfural, which is a product of acid-catalyzed xylose dehydration, making it one of the raw materials of biorefinery transformations. Furoic acid (**1**) was synthesized using the previously described methodology [65] based on the oxidation of furfural (**8**). Using 30% aqueous hydrogen peroxide solution instead of *tert*-butyl hydrogen peroxide in the presence of copper(I) chloride as a catalyst resulted in 38% of yield (see ESI, Scheme S1, panel a). Replacement of the catalyst and using copper(II) bromide instead of copper(I) chloride and *tert*-butyl hydroperoxide [66] (see ESI, Scheme S1, panel b) resulted in the same yield (38%) as previously. The furfurylamine (**2**) was obtained in the described one-pot two-step reductive amination procedure [62] (see ESI, Scheme S2), using furfural (**8**) and hydroxylammonium chloride in the presence of $Na_2CO_3$ in an aqueous medium. In the second stage, furfuryloxime **10** was reduced to furfurylamine (**2**), with zinc dust, $NH_4Cl$, and $ZnCl_2$ as reducing agents at 60 min with 76% of yield (optimization see ESI, Table S1). The last stage of our work on the synthesis of furfural derivatives focused on 2,5-furandicarboxylic acid (**4**). The key intermediate in this synthesis was furan-2,5-dicarboxaldehyde (**9**) [63]. This compound was obtained in a three-step synthesis process (see ESI, Scheme S3), where in the first stage, 2-(2-furanyl)-1,3-dioxolane (**11**) was obtained after short optimization with 82% of yield (optimization see ESI, Table S2). The use of solvents with lower boiling points than toluene reduces the extent of furfural polymerization and thus increases the efficiency of the reaction. Then, the lithium diisopropylamide (LDA) was prepared by treating *n*-butyllithium with diisopropylamine in tetrahydrofuran (THF) was using. Given in the publication temp. −80°C has been changed to −30°C (easier to implement in industrial conditions), which increased the yield from 48 to 61%. The final step was the reaction of 2-(5-formyl-2-furanyl)-1,3-dioxolane (**12**) with a mixture of acetone and 6 N HCl. The furan-2,5-dicarboxaldehyde (**9**) was obtained with a 95% of yield.

Furan-2,5-dicarboxaldehyde (**9**) was used as a substrate to obtain a 52% yield 2,5-furandicarboxylic acid (**4**) by oxidation, with *tert*-butyl hydroperoxide and copper (II) bromide which was used as a catalyst (see ESI, Scheme S1, panel c).

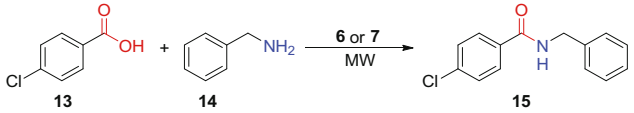
Prior to commencing experiments using the compounds derived from furfural, we optimized the synthesis of model *N*-benzyl-*p*-chlorobenzamide (**15**) formed from 4-chlorobenzoic acid (**13**) and benzylamine (**14**). Optimization conditions were performed using a triazine coupling DMT/NMM/TsO$^-$ (**6**) and a catalytic amount of *N*-methylmorpholine (NMM). NMM is used as a catalyst to convert carboxylic acid to salt. The presence of the carboxylic anion significantly accelerates the triazine ester formation compared to the reaction of the carboxylic acid with DMT/NMM/TsO$^-$. However, it is not advisable to use a stoichiometric amount or excess of NMM, as the formation of carboxylic acid anhydrides is observed, which in turn reduces the efficiency of the condensation reaction

(lower yield of the products). Therefore, it is crucial to use such an amount of NMM to maximize the rate of triazine ester formation while eliminating the formation of anhydrides [67]. The MW conditions (time of reaction), solvents, and amounts of reagent were variable parameters. All experiments are presented in Table 1.

All reactions were performed in a microwave reactor (standard mode, initial 200 W power). In the first stage, the reaction time was optimized. It was found that performing the reaction within 5 min at 90°C resulted in a 66% yield of product **15** (Table 1, Entry 1), using 4-chlorobenzoic acid (**13**) and benzylamine (**14**) as the substrates and DMT/NMM/TsO$^-$ (**6**) in a ratio of 1:1:1, with methylene chloride (DCM) as a solvent. Increasing the time to 10 min increased the yield up to 73% (Table 1, Entry 2). However, further extension of the time to 30 min led to a decrease in the yield to 65% (Table 1, Entry 3). Thus, time 10 min was considered the most optimal. Next, we examined the influence of the solvent on the reaction yield. The replacement of DCM with acetonitrile (ACN) slightly decreased the yield to 72% (Table 1, Entry 4). The use of ethyl acetate (EtOAc), tetrahydrofuran (THF), or toluene enabled the synthesis of final compound **15** with satisfactory but lower yields (69–55%) (Table 1, Entries 5–7). Reaction without solvent gave amide **15** with 44% yield (Table 1, Entry 8). It was decided that DCM would be used in further studies. Increasing the amount of benzylamine (**14**) to 1.5 equiv. decreased the yield to 61% (Table 1, Entry 9). In contrast, increasing the amounts of 4-chlorobenzoic acid (**13**) and DMT/NMM/TsO$^-$ (**6**) to 1.3 equiv. increased the yield of product **15** to 88% (Table 1, Entry 10). Further increasing the amount of carboxylic acid **13** and coupling reagent **6** to 1.5 and 2.0 equiv. did not improve the reaction yield. As would be expected, performing the reaction without coupling reagent resulted in a lack of amide **15** (Table 1, Entry 11). EDC was also used as a coupling reagent. Replacing DMT/NMM/TsO$^-$ (**6**) with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, **7**) resulted in a lower yield of 54% (Table 1, Entry 12). Thus, DMT/NMM/TsO$^-$ (**6**) appears to be a much more effective reagent for the preparation of amide than EDC under microwave-assisted conditions.

Before the synthesis of the target amides and esters derived from furfural, we used the optimized conditions to synthesize amides protected with *N*-Boc-, *N*-Cbz-, and *N*-Fmoc-L-phenylalanine (**16a**–**c**) (Table 2), as well as benzylamine (**14**). In all experiments, the ratio of *N*-protected amino acids **16a**–**c** to amine **14** and coupling agent **6** was 1.3:1:1.3 equiv. After crystallization, the final amides **17a**–**b** were synthesized smoothly with yields of 83% and 88%, respectively (Table 2, Entries 1 and 2). The application of optimal conditions for the synthesis of amide **17c** resulted in a low yield of 35% (Table 2, Entry 3). The low yield of amide **17c** may have resulted from the

**Table 1:** Optimization of the synthesis of *N*-benzyl-*p*-chlorobenzamide (**15**)[a]

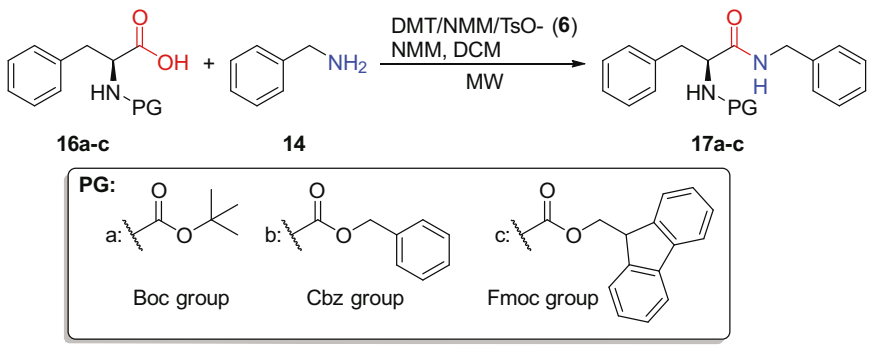



**13** **14** **15**

| Entry | MW conditions[b] | | Solvent[c] | Coupling reagent | Ratio of substrates [equiv.] | Yield of 15 [%][d] |
|---|---|---|---|---|---|---|
| | Time [min] | Temp [°C] | | | 13:14:6 (or 7) | |
| 1 | 5 | 90 | DCM | **6** | 1:1:1 | 66 |
| 2 | 10 | 90 | DCM | **6** | 1:1:1 | 73 |
| 3 | 30 | 90 | DCM | **6** | 1:1:1 | 65 |
| 4 | 10 | 90 | ACN | **6** | 1:1:1 | 72 |
| 5 | 10 | 90 | EtOAc | **6** | 1:1:1 | 69 |
| 6 | 10 | 90 | THF | **6** | 1:1:1 | 67 |
| 7 | 10 | 90 | Toluene | **6** | 1:1:1 | 55 |
| 8 | 10 | 90 | — | **6** | 1:1:1 | 44 |
| 9[e] | 10 | 90 | DCM | **6** | 1:1.5:1 | 61 |
| 10 | 10 | 90 | DCM | **6** | 1.3:1:1.3 | 88 |
| 11 | 10 | 90 | DCM | — | 1.3:1:0 | 0 |
| 12 | 10 | 90 | DCM | **7** | 1.3:1:1.3 | 54 |

[a] 10 mL pressure vial, amount of compound **14** (2 mmol), NMM (0.3 equiv.) relative to compound **6**. [b] Standard mode – 200 W. [c] Amount of solvent (3 mL). [d] Yield after crystallization (ethyl acetate/hexane). [e] Amount of compound **14** (3 mmol).

**Table 2:** Synthesis of *N*-protected amides **17a–c**




| Entry | MW conditions[a] | | Substrate/PG | Yield of 17 [%][b] |
|---|---|---|---|---|
| | Time [min] | Temp [°C] | | |
| 1[c] | 10 | 90 | **16a**/Boc | **17a**/83 |
| 2[c] | 10 | 90 | **16b**/Cbz | **17b**/88 |
| 3[d] | 10 | 90 | **16c**/Fmoc | **17c**/35 |
| 4[d] | 30 | 90 | **16c**/Fmoc | **17c**/65 |
| 5[d] | 40 | 90 | **16c**/Fmoc | **17c**/73 |

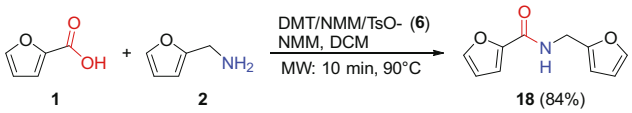
[a] Standard mode – 200 W. [b] Yield after crystallization (ethyl acetate/hexane). [c] 10 mL pressure vial, conditions: *N*-protected amino acids **16a–b** (2.6 mmol), benzylamine (**14**) (0.22 mL, 2 mmol), DMT/NMM/TsO$^-$ (**6**) (1.076 g, 2.6 mmol), NMM (0.09 mL, 0.78 mmol). [d] 10 mL pressure vial, conditions: *N*-protected amino acid **16c** (1.3 mmol), benzylamine (**14**) (0.11 mL, 1 mmol), DMT/NMM/TsO$^-$ (**6**) (0.538 g, 1.3 mmol), NMM (0.045 mL, 0.39 mmol).

lower solubility of **16c**, as well as from greater steric hindrance due to the presence of the fluorene moiety in the Fmoc group, which impeded access by the coupling reagent. Lengthening the reaction time to 30 min or 40 min resulted in increased yields after crystallization to 65% and 73%, respectively (Table 2, Entries 4 and 5).

Having found that DMT/NMM/TsO$^-$ (**6**) is also an effective reagent for the synthesis of amides derived from *N*-protected phenylalanine under microwave-assisted conditions, we began research into the synthesis of amide and ester derivatives containing a furan ring. Initially, the optimal conditions were used to synthesize amide **18** using 2-furoic acid (**1**) and furfurylamine (**2**). The reaction was carried out under MW conditions (10 min, 90°C) in a 10-mL pressure vial in DCM with DMT/NMM/TsO$^-$ (**6**) as the coupling reagent. The ratio of the equiv. of acid **1** to amine **2** and coupling reagent **6** was 1.3:1:1.3. *N*-(Furan-2-ylmethyl) furan-2-carboxamide (**18**) was obtained after crystallization, with 84% yields (Scheme 1).

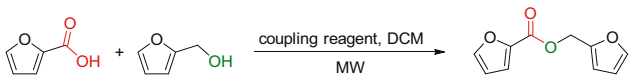
In the next stage, 2-furoic acid (**1**), furfuryl alcohol (**3**), and DMT/NMM/TsO$^-$ (**6**) were used to form the ester bond. Application of the optimal conditions (Table 1, Entry 10) resulted in the expected $^1$H NMR spectrum signals from the final compound **19** as well as unreacted alcohol **3** in a ratio of 1.0:1.4 (Table 3, Entry 1).

In addition to signals from **19** and **3**, signals from unreacted DMT/NMM/TsO$^-$ (**6**) were also observed on the $^1$H NMR spectrum. Elongation of the reaction time to 30 min led to increased conversion of ester **19** and a reduction in the ratio of unreacted alcohol **3** from 1.0:1.4 to 1.0:0.7 (Table 3, Entry 2). The mixture of ester **19** and substrate **3** was purified by flash chromatography, and the final product furan-2-ylmethyl furan-2-carboxylate (**19**) was isolated with 49% yield (Table 3, Entry 2, footnote e). Performing the synthesis of ester **19** for 30 min at 90°C with an excess of 2-furoic acid (**1**) (1.3 equiv.) and DMT/NMM/TsO$^-$ (**6**) (1.6 equiv.) did not improve the conversion of ester **19** (Table 3, Entry 3). To improve the conversion of product **19**, it was decided to replace DMT/NMM/TsO$^-$ (**6**) with EDC (**7**). Although EDC was not as effective as DMT/NMM/TsO$^-$ in terms of amide bond formation, it was definitely more effective for the




**Scheme 1:** Synthesis of *N*-(furan-2-ylmethyl)furan-2-carboxamide (**18**).

**Table 3:** Optimization of the synthesis of furan-2-ylmethyl furan-2-carboxylate (**19**)[a]




1 3 19

| Entry | MW conditions[b] | | Ratio of substrates [equiv.] | Coupling reagent [equiv.] | Ratio of compounds in crude product[c] | Yield of **19** [%][h] |
|---|---|---|---|---|---|---|
| | Time [min] | Temp [°C] | **1**:**3** | | **19**:**3** | |
| 1[d] | 10 | 90 | 1.3:1 | DMT/NMM/TsO$^-$ (**6**) [1.3 equiv.] | 1.0:1.4 | —[i] |
| 2[d,e] | 30 | 90 | 1.3:1 | DMT/NMM/TsO$^-$ (**6**) [1.3 equiv.] | 1.0:0.7 | 49 |
| 3[d] | 30 | 90 | 1.3:1 | DMT/NMM/TsO$^-$ (**6**) [1.6 equiv.] | 1.0:0.8 | —[i] |
| 4 | 30 | 90 | 1.3:1 | EDC (**7**) [1.3 equiv.] | 1.0:0.7 | —[i] |
| 5 | 30 | 90 | 2:1 | EDC (**7**) [2 equiv.] | 1.0:0.4 | —[i] |
| 6[f] | 30 | 90 | 3:1 | EDC (**7**) [3 equiv.] | 1.0:0.0 | 71 |
| 7[d,g] | 30 | 90 | 3:1 | DMT/NMM/TsO$^-$ (**6**) [3 equiv.] | 1.0:2.4 | —[i] |

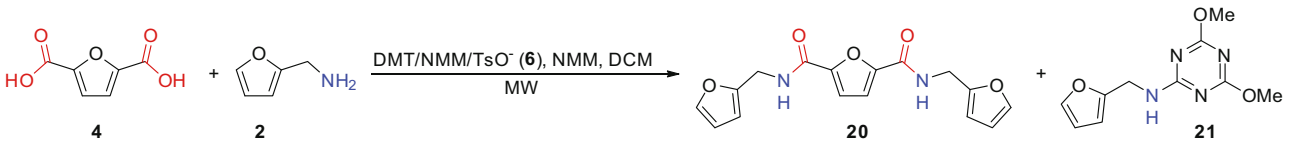
[a] 10 mL pressure vial, amount of compound **3** (2 mmol), DCM (3 mL). [b] Standard mode – 200 W. [c] Based on $^1$H NMR. [d] Catalytic amount of NMM (0.3 equiv.) relative to compound **6**. [e] Yield of product **19** after flash chromatography (hexane/ethyl acetate 10:1) – 49%. [f] Yield of product **19** after flash chromatography (hexane/ethyl acetate 10:1) – 71%. [g] Amount of compound **3** (0.5 mmol). [h] Yield after flash chromatography. [i] Reaction not purified by flash chromatography.

formation of ester bonds. Application of the optimal conditions (1.3 equiv. of 2-furoic acid (**1**), 1 equiv. of furfuryl alcohol (**3**), 1.3 equiv. of EDC for 30 min at 90°C) resulted in a ratio of product **19** to unreacted furfuryl alcohol (**3**) of 1.0:0.7 (Table 3, Entry 4). Increasing the amount of 2-furoic acid (**1**) and EDC to 2 equiv. caused a reduction in the amount of unreacted alcohol (Table 3, Entry 5), whereas using 3 equiv. of carboxylic acid **1** and EDC (**7**) resulted in a lack of furfuryl alcohol (**3**) on the $^1$H NMR spectrum (Table 3, Entry 6). Furan-2-ylmethyl furan-2-carboxylate (**19**) was isolated by flash chromatography with a 71% yield (Table 3, Entry 6, footnote f). Replacement of EDC with DMT/NMM/TsO$^-$ and use of the best conditions (Table 3, Entry 6) resulted in the worse conversion of product **19** and an increased amount of unreacted alcohol (Table 3, Entry 7).

Compounds with diamides and diester bonds are another interesting group of furan derivatives. We first synthesized *N*,*N*-bis(furan-2-ylmethyl)furan-2,5-dicarboxamide (**20**) using furfurylamine (**2**) and 2,5-furandicarboxylic acid (**4**). Reactions were carried out in a microwave reactor in the presence of DMT/NMM/TsO$^-$ (**6**) and NMM. The optimized conditions for these reactions are presented in Table 4.

Application of a double excess of furfurylamine (**2**) and coupling reagent **6** relative to 2,5-furandicarboxylic acid (**4**) (1 mmol) for 10 min at 90°C resulted in a mixture of product **20** and an unidentified compound visible on the $^1$H NMR spectrum. The ratio of the product and side product in the crude mixture was 52%:48% based on $^1$H NMR. Purification by flash chromatography resulted in the isolation of pure product **20** with a 20% yield and of the side product *N*-(furan-2-ylmethyl)-4,6-dimethoxy-1,3,5-triazin-2-amine (**21**) with a yield of 25% (Table 4, Entry 1). Purification by crystallization (in a repeated reaction) resulted in the same yield of product **20**. However, the product was contaminated by the by-product. The ratio of compounds **20**:**21** was 75:25% based on $^1$H NMR (Table 4, Entry 1, footnote e). Further optimization was performed to improve the yield of product **20** and reduce the amount of side product **21**. Using equimolar amounts of amine **2**, dicarboxylic acid **4**, and coupling agent **6** under the same MW conditions resulted in a lower amount of side product **21**. The ratio of compounds **20**:**21** in the crude mixture was 82%:18% based on $^1$H NMR. The yield of *N*,*N*-bis(furan-2-ylmethyl)furan-2,5-dicarboxamide (**20**) after crystallization was 20%, and the product was clean (Table 4, Entry 2). Increasing the amounts of DMT/NMM/TsO$^-$ (**6**) and 2,5-furandicarboxylic acid (**4**) to 1.5 equiv. resulted in the presence of almost no side product **21**. The yield of diamide **20** after crystallization was 37% (Table 4, Entry 3). Further

**Table 4:** Optimization of the synthesis of *N*,*N*-bis(furan-2-ylmethyl)furan-2,5-dicarboxamide (**20**)[a]



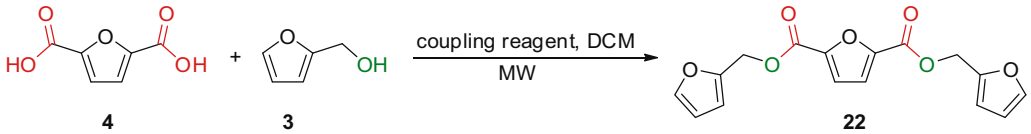

4 2 20 21

| Entry | Ratio of substrates [equiv.] | MW conditions[b] | | Ratio of compounds [%][c] | Yield of 20 [%][d] |
|---|---|---|---|---|---|
| | 4:2:6 | Time [min] | Temp [°C] | 20:21 | |
| 1 | 0.5:1:1 | 10 | 90 | 52:48 | 20[e] |
| 2 | 1:1:1 | 10 | 90 | 82:18 | 20 |
| 3 | 1.5:1:1.5 | 10 | 90 | 94:6 | 37 |
| 4 | 1.5:1:1.5 | 30 | 90 | 86:14 | 31 |
| 5[f] | 1.5:1:1.5 | 10 | 90 | 100:0 | 19 |
| 6[g] | 1.5:1:1.5 | 10 | 90 | 100:0 | 22 |
| 7 | 0.65:1:0.65 | 10 | 90 | 34:66 | 8 |

[a] 10 mL pressure vial, amount of compound **2** (2 mmol), DCM (3 mL), catalytic amount of NMM (0.3 equiv.) relative to compound **6**. [b] Standard mode – 200 W. [c] Based on $^1$H NMR. [d] Yield after crystallization (hexane/ethyl acetate). [e] Product **20** contaminated by side-product **21** (25% of **21** based on $^1$H NMR). [f] DCM replacement by ACN. [g] DCM replacement by DMF.

increasing the amounts of compounds **4** and **6** did not improve the yield of product **20**. When the reaction time was increased to 30 min with the application of 1 equiv. of amine **2**, 1.5 equiv. of dicarboxylic acid **4**, and reagent **6**, the amount of side product **21** in the crude mixture increased and the yield of product **20** decreased to 31% (Table 4, Entry 4). Replacing DCM with ACN or DMF (Table 4, Entries 5 and 6) resulted in the presence of no side product **21** in the crude mixture. However, the yields of *N*,*N*-bis(furan-2-ylmethyl)furan-2,5-dicarboxamide (**20**) were lower (19 and 22%, respectively). Application of the conditions used for the synthesis of the monoamide **18** resulted to obtain a mixture of product **20** and side product **21** in a ratio of 34:66% based on $^1$H NMR. After crystallization, the final product **20** was isolated with a low yield (8%) (Table 4, Entry 7).

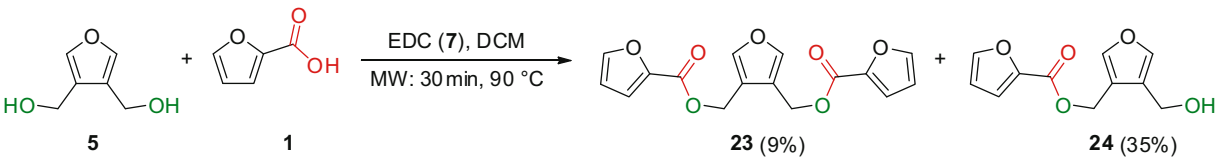
**Table 5:** Optimization of the synthesis of bis(furan-2-ylmethyl)furan-2,5-dicarboxylate (**22**)[a]




4 3 22

| Entry | Ratio of substrates [equiv.] | MW conditions[b] | | Coupling reagent [equiv.] | Ratio of compounds in crude product[c] | Yield of 22 [%][f] |
|---|---|---|---|---|---|---|
| | 4:3 | Time [min] | Temp [°C] | | 22:3 | |
| 1[d] | 1.5:1 | 30 | 90 | DMT/NMM/TsO⁻ (**6**) [1.5 equiv.] | 1.0:3.7 | —[g] |
| 2 | 0.5:1 | 30 | 90 | EDC (**7**) [1 equiv.] | 1.0:4.0 | —[g] |
| 3 | 1:1 | 30 | 90 | EDC (**7**) [2 equiv.] | 1.0:1.6 | —[g] |
| 4[e] | 1.5:1 | 30 | 90 | EDC (**7**) [3 equiv.] | 1.0:0.8 | 7 |
| 5[d] | 1.5:1 | 30 | 90 | DMT/NMM/TsO⁻ (**6**) [3 equiv.] | 1.0:1.4 | —[g] |
| 6 | 1.5:1 | 30 | 90 | EDC (**7**) [1.5 equiv.] | 1.0:2.1 | — |

[a] 10 mL pressure vial, amount of compound **3** (1 mmol), DCM (3 mL). [b] Standard mode – 200 W.· [c] Based on $^1$H NMR. [d] Compound **3** (1 mmol), catalytic amount of NMM (0.3 equiv.) relative to compound **6**. [e] Yield of product **22** after flash chromatography (hexane/ethyl acetate 3:1) – 7%. [f] Yield after flash chromatography. [g] Reaction not purified by flash chromatography.




**Scheme 2:** Synthesis of furan-3,4-diylbis(methylene)bis(furan-2-carboxylate) (**23**).

The synthesis of compounds with diesters bonds – bis(furan-2-ylmethyl) furan-2,5-dicarboxylate (**22**) and furan-3,4-diylbis(methylene) bis(furan-2-carboxylate) (**23**) – was more problematic. First, we performed the synthesis of bis(furan-2-ylmethyl) furan-2,5-dicarboxylate (**22**). Under the optimal conditions applied for the synthesis of *N*,*N*-bis(furan-2-ylmethyl)furan-2,5-dicarboxamide (**20**) (Table 4, Entry 3), using 1 equiv. of furfuryl alcohol (**3**) and 1.5 equiv. of both 2,5-furandicarboxylic acid (**4**) and DMT/NMM/TsO$^-$ (**6**) for 30 min at 90°C resulted in $^1$H NMR spectrum signals from final compound **22**, as well as unreacted alcohol **3** in a ratio of 1.0:3.7. However, the attempt to isolate product **22** using flash chromatography failed (Table 5, Entry 1). Because EDC was more effective for forming ester bonds than DMT/NMM/TsO$^-$ (see Table 3), subsequent experiments were conducted using EDC. Using a double excess of alcohol **3** and EDC relative to dicarboxylic acid **4** (1 mmol) resulted that the ratio of product **22** to unreacted alcohol was 1.0:4.0 (Table 5, Entry 2). Increasing the amount of dicarboxylic acid **4** to 1 equiv. or 1.5 equiv., with 2 equiv. or 3 equiv. of EDC, respectively, resulted in a decrease in the amount of unreacted alcohol **3** on the $^1$H NMR spectrum (Table 5, Entries 3 and 4). Because further attempts to increase the amount of acid **4** did not contribute to reducing the amount of unreacted alcohol **3**, bis(furan-2-ylmethyl) furan-2,5-dicarboxylate (**22**) was isolated by flash chromatography with a low yield (Table 5, Entry 4, footnote e). The low yield of product **22** was also due to the presence of many unidentified compounds. Application of the optimal conditions (Table 5, Entry 4) and the replacement EDC with DMT/NMM/TsO$^-$increased the amount of unreacted alcohol. The ratio of product **22** to unreacted alcohol **3** was 1.0 to 1.4 (Table 5, Entry 5). Applying the conditions used to synthesis of monoester **19** did not improve the ratio of product **22** to unreacted alcohol (Table 5, Entry 6).

The second compound with two ester bonds, furan-3,4-diylbis(methylene) bis(furan-2-carboxylate) (**23**), was synthesized using 3,4-bis(hydroxymethyl)furan (**5**). Given that EDC was responsible for better conversion of product **22**, EDC was also used for the synthesis of diester **23** (Scheme 2). Performing the reaction with 2 equiv. of 2-furoic acid (**1**), 1 equiv. of 3,4-bis(hydroxymethyl)furan (1 mmol) (**5**), and 2 equiv. of coupling reagent EDC (**7**) for 30 min at 90°C resulted in an excess of monoester (4-(hydroxymethyl)furan-3-yl)methyl furan-2-carboxylate (**24**), which was isolated by flash chromatography with 35% yield.

Final product **23** was isolated after flash chromatography and preparative thin-layer chromatography (PTLC) with 9% yield (Scheme 2).

## 4 Conclusion

In summary, this study shows that furfural derivatives containing one functional group – 2-furoic acid (**1**), furfurylamine (**2**), furfuryl alcohol (**3**), as well as the disubstituted furan derivatives 2,5-furandicarboxylic acid (**4**) and 3,4-bis(hydroxymethyl)furan (**5**) – can be used as starting materials for the synthesis of new amides and esters using classical coupling reagents under mild conditions, supported by microwave radiation. Five final compounds containing furan rings were synthesized using a microwave reactor in the presence of DMT/NMM/TsO$^-$ (**6**) or EDC (**7**) as a coupling agent. Two compounds with single amide and ester bonds, *N*-(furan-2-ylmethyl)furan-2-carboxamide (**18**) and furan-2-ylmethyl furan-2-carboxylate (**19**), were obtained with yields of 84% and 49%, respectively, using DMT/NMM/TsO$^-$. Additionally, ester **19** was obtained with 71% yield in the presence of EDC. Three compounds with two amide and ester bonds were also synthesized. *N*,*N*-Bis(furan-2-ylmethyl)furan-2,5-dicarboxamide (**20**) with two amide bonds was obtained with 37% yield using DMT/NMM/TsO$^-$. Bis(furan-2-ylmethyl) furan-2,5-dicarboxylate (**22**) and furan-3,4-diylbis(methylene) bis(furan-2-carboxylate) (**23**), both with two esters bonds, were obtained in the presence of EDC with only 7% and 9% yields, respectively. Therefore, it can be concluded that both coupling agents (DMT/NMM/TsO$^-$ and EDC) are efficient for the synthesis of amide and ester derivatives containing a furan ring.

DMT/NMM/TsO$^-$ is more effective than EDC for obtaining an amide bond. However, EDC allows higher yields of ester than DMT/NMM/TsO$^-$.

The synthesis of compounds with an amide bond occurred under milder conditions than the synthesis of compounds with an ester bond. During the synthesis of compounds with an ester bond, larger amounts of reagents (carboxylic acid and coupling reagent) and longer reaction times were required, which may have been due to the weaker nucleophilic character of alcohol compared to an amine. The synthesis of compounds with diamide and diester bonds was more difficult. Final compounds were synthesized with moderate or low yields, which may be explained by the lower solubility of substrate 2,5-furandicarboxylic acid (**4**), the greater steric hindrance of dicarboxylic acid **4** and 3,4-bis(hydroxymethyl)furan (**5**), and by competitive reactions leading to the synthesis of the side products *N*-(furan-2-ylmethyl)-4,6-dimethoxy-1,3,5-triazin-2-amine (**21**) and 4-(hydroxymethyl)furan-3-yl) methyl furan-2-carboxylate (**24**). Both side products were isolated and characterized. Whereas diamide **20** was synthesized in the presence of DMT/NMM/TsO$^-$, the synthesis of both diesters **22** and **23** required the use of EDC. Further research is underway to develop reaction conditions for the formation of polyesters and polymers using diacids, diamines, and dialcohols derived from furfural.

**Funding information:** This research was funded by the National Centre for Research and Development under Project BIOSTRATEG2/296369/5/NCBR/2016.

**Conflict of interest:** The authors declare that they have no conflicts of interest.

**Author contributions:** Ł. J. – formal analysis, investigation, methodology, visualization, writing – original draft; D. Z. – investigation; B. K. – conceptualization, funding acquisition, project administration, supervision, writing – review and editing.

**Data availability statement:** All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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