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Synthesis of novel 2,6-bis(5-*t*-butylbenzo[*b*]furan-2-ylcarbonyl)pyridines

Abstract: A facile synthesis of new 2,6-bis(5-*t*-butylbenzo[*b*]furan-2-ylcarbonyl)pyridines **3a–e** is described. The synthesis mainly relies on the ultrasound-assisted Rap-Stoermer reaction of 2,6-bis(bromoacetyl)pyridine (**1**) with *t*-butyl substituted salicylaldehydes **2a–e** in MeCN with the presence of PEG-400 as catalyst. This procedure is characterized by short reaction times and good yields.

Keywords: benzofuran; methanone; pyridine; Rap-Stoermer reaction; *t*-butyl; ultrasound-assisted.

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Introduction

2,6-Diheteroaryl-containing pyridines have been widely investigated and reported to display important biological properties such as antitumor and CDK inhibitory activities (Fichera et al., 2000, 2002; Barresi et al., 2002). As an example, 2,6-bis[(furan-2-yl)vinyl]pyridine where the three heteroaromatic rings are linked by two ethylenic moieties is a potent inhibitor of the growth of MCF7 breast carcinoma cells (Barresi et al., 2002; Fichera et al., 2002). In addition, the potential applications of complexes of 2,6-diheteroaryl-containing pyridines with transition metal ions in molecular photochemical devices for energy conversion and as fluorescent binding agents for DNA have been studied extensively in recent years (Jäger et al., 2007; Fortuna et al., 2010; Hurtado et al., 2011). Consequently, practical and diverse approaches to the synthesis of new types of 2,6-diheteroaryl-containing pyridine derivatives are of interest (Davies et al., 1996; Brien et al., 2006; Duncan and Garner, 2011).

By contrast, the benzofuran system is an important substructure in a number of molecules that exhibit an array of biological and pharmacological activities. In particular, compounds containing a carbonyl linker between the aromatic and benzofuran moieties are highly valuable molecular motifs often found in pharmaceutical agents. Such compounds have been the focus of much attention owing to their wide range of biological properties, such as antitumor (Hayakawa et al., 2004), antimicrobial (Alper-Hayta et al., 2008), anticonvulsant, anti-inflammatory (Dawood et al., 2006), and antifungal (Romagnoli et al., 2009) activities. It is a small wonder therefore that in recent years the synthesis of new benzofuran-2-yl-carbonyl-substituted heteroaromatic compounds appear frequently in the literature (Parekh et al., 2011).

In addition, the introduction of *tert*-butyl group into some heterocycles can greatly enhance their biological activity (Moreau et al., 2006; Huy et al., 2007; Murakata and Kimura, 2010). For example, it has recently been reported (Huy et al., 2007) that the placement of a metabolically stable *tert*-butyl group at C-2 position of a quinolone system in primaquine results in a tremendous improvement in blood schizontocidal antimalarial activity. Furthermore, the introduction of *tert*-butyl groups into organic molecules increases lipophilicity of the molecule which is very important for passing through the extraordinary thick and light cell wall (Vinsova et al., 2006).

Taking these facts into account and in view of structural diversity which plays a prominent role in medicinal and combinatorial chemistry (Dolle and Nelson, 1999), we found it attractive to construct new prototypes by combining both *tert*-butyl substituent and the carbonyl linker between the benzofuran system and pyridine moiety in the same molecule. Such compounds may be important in the development of new medicinal products with interesting properties.

Results and discussion

Recently, our group has reported on the synthesis of interesting *t*-butyl substituted polycyclic hetero-fused quinoline systems (Li et al., 2009; Li and Gao, 2012). Moreover,

we have gained substantial ability in the synthesis of benzofuran-containing heterocycles through previous experience (Gao et al., 2010, 2011a,b, 2012). Thus, building on this evolving expertise and in diversifying our work on the synthesis of new benzofuran derivatives, our present work is directed towards an extension of this work to include examples of novel heterocyclic compounds containing both *t*-butyl group and a carbonyl linker between the benzofuran system and the pyridine ring (Scheme 1). The starting material, 2,6-bis(bromoacetyl)pyridine (**1**), has been previously synthesized by bromination of 2,6-diacetylpyridine (Deady and Stanborough, 1981). However, no work has been reported on the Rap-Stoermer reaction of **1** with salicylaldehydes. The one-pot Rap-Stoermer reaction of **1** with *t*-butyl substituted salicylaldehydes **2a–e** to give the desired products **3a–e** is shown in Scheme 1.

In a typical experiment, a mixture of substrate **1**, *t*-butyl substituted salicylaldehyde **2**, 15 mol% PEG-400, and K_2CO_3 was sonicated in MeCN at 70°C for 2–5 h. After completion of the reaction, as monitored by TLC, the products were isolated in good yields of 54–81% by silica gel column chromatography. The Rap-Stoermer reaction between **1** and **2a** using the ultrasound-assisted method was compared to the reaction between the same reactants in an oil bath under similar reaction conditions (time and temperature). In the latter case, compound **3a** was afforded in a poor yield of 27%. When the reaction was carried out in MeCN under reflux conditions for 24 h, the yield only improved to 35%. No improvements were observed by an attempted use of other bases and solvents. These results show that ultrasonication efficiently promotes this reaction allowing the synthesis of **3a–e** in relatively short reaction times and good yields. It was also observed that conducting the ultrasonic-assisted Rap-Stoermer reaction in the absence of PEG-400 resulted in greatly lower yields of the products. It is noteworthy that the use of 15 mol% PEG-400 is optimal and any greater amount results in a lower yield.

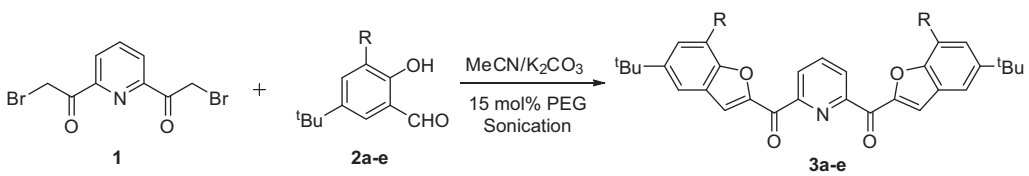
The synthesized compounds **3a–e** are new and their structures were established by spectroscopic and analytical data. For example, the ^{1}H NMR spectrum of compound **3a** exhibits a singlet at 1.35 ppm due to two symmetrical *t*-butyl protons and the absence of the corresponding signal attributable to α-bromoacetyl protons of its precursor **1**. The particular characteristics are the presence of a singlet due to two magnetically equivalent furan protons at 8.36 ppm and the signals for nine aromatic protons between 7.59 and 8.46 ppm. The ^{1}H decoupled ^{13}C NMR spectrum shows the presence of carbonyl carbon atoms at 180.2 ppm, supporting the IR absorption at 1651 cm^{-1}. Finally, the structure of **3a** is fully consistent with the elemental analysis results. The spectral and analytical results of other compounds are also fully consistent with the given structures.

Conclusion

The present investigation demonstrates a ready synthesis of a series of new heterocyclic compounds **3a–e**. Readily availability of starting materials, mild reaction conditions, short reaction times, satisfactory yields, and the use of non-toxic and inexpensive catalyst contribute to the usefulness of this method.

Experimental

The staring materials used in this work were obtained from Fluka and used without purification. Melting points (uncorrected) were determined on a WRS-1B melting points apparatus. Ultrasonication was performed in a KQ-250B medical ultrasound cleaner with a frequency of 40 KHz and output power of 250 W. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Brucker AVANCE NMR spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. The elemental analyses were performed on an EL-III element analyzer. The progress of reactions was monitored by thin layer chromatography (TLC) on silica gel GF254 using ethyl acetate/petroleum ether (1:6) as eluent.



2a, **3a**: R = H; **2b**, **3b**: R = F; **2c**, **3c**: R = Cl; **2d**, **3d**: R = Br; **2e**, **3e**: R = *t*-Bu

Scheme 1 Synthesis of 2,6-bis(5-*t*-butylbenzo[*b*]furan-2-ylcarbonyl)pyridines **(3a-e)**.

General procedure for the ultrasound promoted synthesis of 2,6-bis(5-*t*-butylbenzo[*b*]furan-2-ylcarbonyl)pyridine derivatives 3a–e

A mixture of 2,6-bis(bromoacetyl)pyridine (**1**, 0.4 mmol, 0.13 g), *t*-butyl substituted salicylaldehyde (**2a–e**, 0.8 mmol), acetonitrile (4 mL), potassium carbonate (4 mmol, 0.55 g), and PEG-400 (15 mmol) was sonicated at 70°C for 5 h. After the reaction was completed as monitored by TLC, the mixture was cooled to room temperature, poured into water and filtered to give the crude product, which was then crystallized from 1,4-dioxane.

2,6-Bis(5-*t*-butylbenzo[*b*]furan-2-ylcarbonyl)pyridine (3a) This compound was obtained as white crystals from **2a**; reaction time 5 h; yield 61%; mp 265–267°C; ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 18H), 7.59 (s, 2H), 7.62 (d, 2H, *J* = 8 Hz), 7.63 (d, 2H, *J* = 8 Hz), 8.18 (t, 1H, *J* = 8 Hz), 8.36 (s, 2H), 8.46 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 31.6, 34.8, 111.9, 119.5, 120.5, 127.1, 127.2, 127.5, 138.5, 147.3, 151.2, 153.0, 154.5, 180.2. Anal. Calcd for $C_{31}H_{29}NO_4$: C, 77.64; H, 6.10; N, 2.92. Found: C, 77.75; H, 6.42; N, 2.85.

2,6-Bis(5-*t*-butyl-7-fluorobenzo[*b*]furan-2-ylcarbonyl)pyridine (3b) This compound was obtained as a yellow solid from **2b**; reaction time 5 h; yield 64%; mp 261–263°C; ^{1}H NMR (DMSO-d_6) δ 1.29 (s, 18H), 7.46 (s, 2H), 7.60 (s, 2H), 8.25 (t, 1H, *J* = 8 Hz), 8.40 (s, 2H), 8.43 (d, 2H, *J* = 8 Hz); ^{13}C NMR (DMSO-d_6): δ 31.4, 34.7, 112.2, 121.4, 121.7, 122.5, 128.3, 128.5, 129.0, 139.1, 149.4, 153.5, 155.5, 180.3. Anal. Calcd for $C_{31}H_{27}F_2NO_4$: C, 72.22; H, 5.28; N, 2.72. Found: C, 72.38; H, 5.44; N, 2.90.

2,6-Bis(5-*t*-butyl-7-chlorobenzo[*b*]furan-2-ylcarbonyl)pyridine (3c) This compound was obtained as white crystals from **2c**; reaction time 5 h; yield 67%; mp 270–271°C; ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 18H), 7.47 (d, 2H, *J* = 1 Hz), 7.58 (d, 2H, *J* = 1 Hz), 8.19 (t, 1H, *J* = 8 Hz), 8.30 (s, 2H), 8.46 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 31.5, 35.0, 117.2, 118.2, 120.3, 127.2, 127.4, 128.7, 138.7, 148.8, 150.2, 151.7, 152.8, 180.0. Anal. Calcd for $C_{31}H_{27}Cl_2NO_4$: C, 67.89; H, 4.96; N, 2.55. Found: C, 67.69; H, 5.01; N, 2.68.

2,6-Bis(7-bromo-5-*t*-butylbenzo[*b*]furan-2-ylcarbonyl)pyridine (3d) This compound was obtained as white crystals from **2d**; reaction time 5 h; yield 63%; mp 249–251°C; ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 18H), 7.51 (d, 2H, *J* = 1 Hz), 7.74 (d, 2H, *J* = 1 Hz), 8.20 (t, 1H, *J* = 8 Hz), 8.32 (s, 2H), 8.46 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 31.6, 34.9, 117.5, 118.9, 120.4, 127.3, 127.6, 128.3, 130.2, 138.7, 149.1, 151.6, 152.7, 180.3. Anal. Calcd for $C_{31}H_{27}Br_2NO_4$: C, 58.42; H, 4.27; N, 2.20. Found: C, 58.64; H, 4.36; N, 2.12.

2,6-Bis(5,7-di-*t*-butylbenzo[*b*]furan-2-ylcarbonyl)pyridine (3e) This compound was obtained as a white solid from **2e**; reaction time 5 h; yield 58%; mp 264–266°C; ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 18H), 1.35 (s, 18H), 7.44 (s, 2H), 7.48 (s, 2H), 8.26 (t, 1H, *J* = 8 Hz), 8.35 (s, 2H), 8.48 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$): δ 30.1, 31.4, 34.6, 35.6, 117.3, 119.2, 120.3, 127.1, 127.9, 129.0, 129.8, 138.6, 150.4, 151.5, 152.9, 180.1. Anal. Calcd for $C_{39}H_{45}NO_6$: C, 79.15; H, 7.66; N 2.37. Found: C, 79.36; H, 7.73; N, 2.12.

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