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Synthesis of mono- and bis-1,2,3-triazole derivatives containing 4*H*-pyran-4-one moiety by 1,3-dipolar cycloaddition reaction

Abstract: An efficient and green methodology for the synthesis of 1,2,3-triazoles substituted with a 4*H*-pyran-4-one moiety was developed by treatment of 2-(4-azidomethylphenyl)-6-phenyl-4*H*-pyran-4-one with alkynes in water. The yields are good to excellent. The reactions of the terminal alkynes occur in the presence of Cu(I) as catalyst and lead to the formation of 1,4-disubstituted 1,2,3-triazoles. Also, bis-1,2,3-triazoles containing 4*H*-pyran-4-one moiety were synthesized by the reaction of 2,6-bis[4-(azidomethyl)phenyl]-4*H*-pyran-4-one with internal alkynes in 51–84% yields.

Keywords: bis-1,2,3-triazole; 1,3-dipolar cycloaddition; 4*H*-pyran-4-one; 1,2,3-triazole; water.

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Introduction

1,2,3-Triazoles and their derivatives are an important class of heterocyclic compounds that have broad applications as fungicides, plant growth regulators, dyes, and corrosion inhibitors [1]. 1,2,3-Triazoles have also attracted continued interest to organic and medicinal scientists over the years because of their broad spectrum of biological activities such as antibacterial [2, 3], antiallergic [4], antifungal [5, 6], antiviral [7], and anti-HIV properties [8–10]. These compounds have been synthesized by a variety of methods [11–15], the 1,3-dipolar cycloaddition reaction of organic azides with alkynes being the most widely used [16].

Meanwhile, 4*H*-pyran-4-one and its derivatives are an important class of heterocyclic compounds due to their wide range of biological activities and their presence in naturally occurring compounds [17–20]. They have shown to possess anticancer [21], anti-HIV [22], antileishmanial [23], antimicrobial, and anticonvulsant [24, 25] activities.

In continuation of our works on the synthesis of heterocyclic compounds [26–28], we have recently synthesized a new series of hybrid molecules containing 4*H*-pyran-4-one coupled to 1,2,3-triazole by the reaction of 2-(4-azidomethylphenyl)-6-phenyl-4*H*-pyran-4-one with various alkynes in toluene or acetonitrile in moderate to good yields [29]. In this report, we present an efficient, green, and safe method for the construction of 1,2,3-triazoles containing 4*H*-pyran-4-one moiety in water as a green solvent.

Results and discussion

The starting compounds, 4*H*-pyran-4-one, 2-(4-bromomethylphenyl)-6-phenyl-4*H*-pyran-4-one, and 2,6-bis[4-(bromomethyl)phenyl]-4*H*-pyran-4-one, were prepared according to the literature procedures [30, 31]. 2-(4-Azidomethylphenyl)-6-phenyl-4*H*-pyran-4-one (**1** in Scheme 1) was prepared by the reaction of 2-(4-bromomethylphenyl)-6-phenyl-4*H*-pyran-4-one with NaN_3 in dimethylformamide (DMF) [29]. Initially, we studied the effect of different solvents including ethanol and water on the formation of 1,2,3-triazoles **2** (Scheme 1) by the reaction of azide **1** with disubstituted and monosubstituted alkynes. As shown in Table 1, 1,2,3-triazoles **2a,b** were prepared from disubstituted alkynes most efficiently by the reaction conducted in water. In the case of terminal alkynes, the use of Cu(I) salts is essential. 1,4-Disubstituted 1,2,3-triazoles **2c–2g** were prepared by the reaction of azide **1** with terminal alkynes such as methyl and ethyl acetylenecarboxylates, phenylacetylene, propargyl alcohol, and 3-butyn-1-ol in the presence of CuI in EtOH under reflux conditions in low to moderate yields. However, the same reactions were performed in good to

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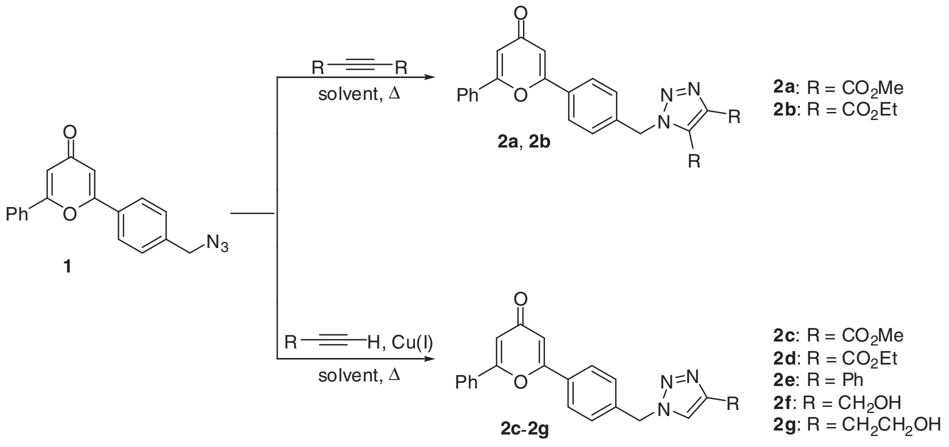


Scheme 1

Table 1: Synthesis of 1,2,3-triazoles containing 4*H*-pyran-4-one moiety in various solvents.

Entry	Alkyne	Product	Method[a,b]	Time (h)	Yield (%)
1	$MeCO_2C{\equiv}CCO_2Me$	**2a**	A	2	71
			B	24	90
			C	1	96
2	$EtCO_2C{\equiv}CCO_2Et$	**2b**	A	2	64
			B	24	71
			C	1	74
3	$HC{\equiv}CCO_2Me$	**2c**	A	4	43
			B	48	65
			C	1	69
4	$HC{\equiv}CCO_2Et$	**2d**	A	4	66
			B	48	56
			C	1	70
5	$HC{\equiv}CPh$	**2e**	A	24	54
			B	48	60
			C	1	63
6	$HC{\equiv}CCH_2OH$	**2f**	A	24	46
			B	48	28
			C	1	55
7	$HC{\equiv}CCH_2CH_2OH$	**2g**	A	24	40
			B	48	27
			C	1	50

[a] Method A: toluene or CH_3CN, reflux, 2–24 h [29]. Method B: EtOH, reflux, 24–48 h. Method C: H_2O, 100°C, 1 h.

[b] For the synthesis of 1,2,3 triazoles **2c–2g**, Cu(I) was used as a catalyst.

excellent yields in the presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in water. All compounds **2a–2g** were characterized by melting point, FT-IR, ^1H NMR, ^{13}C NMR, and by comparison with literature data [29].

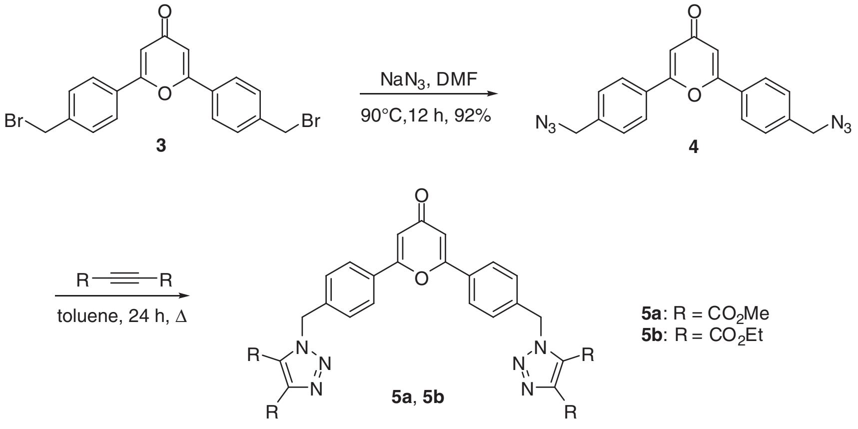
2,6-Bis[4-(azidomethyl)phenyl]-4*H*-pyran-4-one (**4**) was synthesized by the reaction of 2,6-bis[4-(bromomethyl) phenyl]-4*H*-pyran-4-one (**3**) with sodium azide in dry DMF (Scheme 2). The structure of azide product **4** is fully consistent with its spectroscopic data. The FT-IR spectrum of the compound **4** shows a strong absorption band at 2102 cm^{-1} corresponding to the azide group. Bis-1,2,3-triazoles **5a** and **5b** were synthesized by the reaction of compound **4** with dimethyl and diethyl acetylenedicarboxylates in the respective yields of 51% and 84%.

Conclusions

In the present work, we described an efficient, green, and safe method for the preparation of 1,2,3-triazoles by the reaction of 2-(4-azidomethylphenyl)-6-phenyl-4*H*-pyran-4-one with various alkynes in moderate to excellent yields. It was found that the use of water as green solvent in 1,3-dipolar cycloaddition reaction of 2-(4-azidomethylphenyl)-6-phenyl-4*H*-pyran-4-one with alkynes increases the reaction yield and reduces the reaction time in comparison to the same reaction in other solvents such as toluene, acetonitrile, and ethanol. Also, bis-triazoles were synthesized by the reaction of 2,6-bis[4-(azidomethyl)phenyl]-4*H*-pyran-4-one with internal alkynes in moderate to good yields.

Experimental

All reagents were purchased from Merck or Fluka companies and were used without further purification. The completion of the reactions and purity of the compounds were followed by thin-layer chromatography (TLC) on silica gel 60 HF$_{254}$, with detection by UV light. Crude products were purified by crystallization or preparative layer chromatography (PLC; Merck, silica gel 60 F$_{254}$, CAMAG, Switzerland). FT-IR spectra were obtained using KBr pellets on a tensor 27-Bruker spectrometer (Shimadzu, Japan). ^1H NMR and ^{13}C NMR spectra were



Scheme 2

recorded on a FT-NMR Bruker spectrometer at 400 and 100 MHz, respectively, in CDCl$_3$ or DMSO-d_6. Mass spectra were recorded using a direct insert probe of Agilent Technologies 5975c mass spectrometer. Elemental analyses were carried out on Perkin-Elmer CHNS-O Analyzer, Model 2400 Series II.

General procedure for the preparation of triazoles 2a,b

To a solution of 2-(4-azidomethylphenyl)-6-phenyl-4*H*-pyran-4-one (**1**, 0.1 g, 0.33 mmol) in toluene [29], ethanol or water (10 mL) was added dimethyl or diethyl acetylenedicarboxylate (0.99 mmol), and the mixture was heated under reflux for 1–24 h (monitored by TLC). During this time, the triazole precipitated. The precipitate was collected by filtration, dried *in vacuo*, and crystallized from EtOH.

Dimethyl 1-[4-(4-oxo-6-phenyl-4*H*-pyran-2-yl)benzyl]-1,2,3-triazole-4,5-dicarboxylate (2a): White solid; mp 186–187°C; ^{13}C NMR (CDCl$_3$): δ 51.8, 52.4, 52.5, 110.5, 110.9, 124.9, 125.5, 127.8, 128.2, 128.3, 130.3, 130.5, 131.0, 136.2, 139.6, 157.7, 159.3, 161.4, 162.4, 179.0 (pyrone C=O) ppm.

Diethyl 1-[4-(4-oxo-6-phenyl-4*H*-pyran-2-yl)benzyl]-1,2,3-triazole-4,5-dicarboxylate (2b): White solid; mp 146–147°C; ^{13}C NMR (CDCl$_3$): δ 12.8, 13.1, 52.2, 61.0, 61.9, 110.5, 110.8, 124.9, 125.4, 127.7, 128.2, 128.4, 130.2, 130.5, 130.9, 136.3, 139.8, 157.3, 159.0, 161.3, 162.4, 179.0 (pyrone C=O) ppm.

General procedure for the preparation of 1,4-disubstituted 1,2,3-triazoles 2c–2g

Method A: To a solution of 2-(4-azidomethylphenyl)-6-phenyl-4*H*-pyran-4-one (**1**, 0.1 g, 0.33 mmol) and terminal alkyne (0.99 mmol) in dry acetonitrile (12 mL) was added 10 mol% CuI. The mixture was heated under reflux for 2–24 h, and the reaction was monitored by TLC. After completion of the reaction, the resulting precipitate was collected by filtration and dried *in vacuo* [29].

Method B: To a solution of compound **1** (0.1 g, 0.33 mmol) and terminal alkyne (0.99 mmol) in EtOH (10 mL) was added 10 mol% CuI. The mixture was heated under reflux for 24–48 h, and progress of the reaction was monitored by TLC. After completion of the reaction, the resulting precipitate was collected by filtration and dried under reduced pressure.

Method C: To a solution of compound **1** (0.1 g, 0.33 mmol) and terminal alkyne (0.99 mmol) in water (12 mL) were added 10 mol% CuSO$_4$·5H$_2$O and 5 mol% sodium ascorbate. The mixture was heated at 100°C for 1 h, and progress of the reaction was monitored by TLC. After completion of the reaction, the resulting precipitate was collected by filtration and dried under reduced pressure.

Methyl 1-[4-(4-oxo-6-phenyl-4*H*-pyran-2-yl)benzyl]-1,2,3-triazole-4-carboxylate (2c): White solid; mp 211–212°C (from EtOH); ^{13}C NMR (CDCl$_3$): δ 51.3, 52.8, 110.5, 110.9, 124.9, 125.8, 126.5, 127.8, 128.2, 130.2, 130.6, 131.3, 136.0, 139.5, 159.9, 161.2, 162.4, 179.0 (pyrone C=O) ppm.

Ethyl 1-[4-(4-oxo-6-phenyl-4*H*-pyran-2-yl)benzyl]-1,2,3-triazole-4-carboxylate (2d): Creamy solid; mp 191–192°C (from EtOH); ^{13}C NMR (CDCl$_3$): δ 13.2, 52.8, 60.4, 110.5, 110.9, 124.9, 125.8, 126.4, 127.8, 128.2, 130.2, 130.5, 131.3, 136.1, 139.9, 159.5, 161.2, 162,4, 179.0 (pyrone C=O) ppm.

2-Phenyl-6-{[4-(4-phenyl-1,2,3-triazol-1-yl)methyl]phenyl}-4*H*-pyran-4-one (2e): Light yellow solid; mp 128–130°C (from CHCl$_3$); ^{13}C NMR (CDCl$_3$): δ 52.6, 110.5, 110.8, 118.6, 124.7, 124.9, 125.7, 127.3, 127.6, 127.8, 128.0, 128.2, 129.3, 130.3, 130.5, 131.0, 137.1, 161.4, 162.4, 179.0 (pyrone C=O) ppm.

2-{4-[(4-Hydroxymethyl-1,2,3-triazol-1-yl)methyl]phenyl}-6-phenyl-4*H*-pyran-4-one (2f): This compound was purified by PLC on silica gel using *n*-hexane/acetone (2:1) as eluent; white solid; mp 190–191°C; ^{13}C NMR (DMSO-d_6): δ 52.3, 55.1, 110.9, 111.1, 123.1, 126.1, 126.6, 128.6, 129.3, 130.7, 130.9, 131.6, 139.7, 148.5, 162.0, 162.5, 179.0 (pyrone C=O) ppm.

2-{4-[(4-(2-Hydroxyethyl)-1,2,3-triazol-1-yl)methyl]phenyl}-6-phenyl-4*H*-pyran-4-one (2g): This compound was purified by PLC on silica gel using *n*-hexane/acetone (2:1) as eluent; white solid; mp 186–187°C; ^{13}C NMR (DMSO-d_6): δ 29.2, 52.2, 60.3, 110.9, 111.1, 122.9, 126.1, 126.5, 128.5, 129.2, 130.7, 130.9, 131.5, 139.7, 144.9, 162.0, 162.4, 179.0 (pyrone C=O) ppm.

2,6-Bis[4-(azidomethyl)phenyl]-4*H*-pyran-4-one (4): To a solution of 2,6-bis[4-(bromomethyl)phenyl]-4*H*-pyran-4-one (**3**, 1 g, 2.3 mmol) in dry dimethylformamide (20 mL) was added sodium azide (0.3 g, 5 mmol), and the mixture was heated at 90°C for 12 h. After completion of the reaction, as monitored by TLC, the mixture was cooled to room temperature and diluted with cold water. The resulting precipitate was filtered off, washed with water, and dried *in vacuo* to give azide **4** as a white solid; yield 0.76 g (92%); mp 121–122°C; FT-IR: 3064, 2881, 2102 (N$_3$), 1649 (pyrone C=O), 1515, 1419, 1382, 1263, 1078, 945 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 4.46 (s, 4H, -CH$_2$-), 6.83 (s, 2H, pyrone-H), 7.50 (d, 4H, *J* = 8.2 Hz, Ar-H), 7.88 (d, 4H, *J* = 8.2 Hz, Ar-H) ppm; ^{13}C NMR (CDCl$_3$): δ 53.2, 110.7, 125.5, 127.8, 130.4, 138.0, 161.8, 179.0 (pyrone C=O) ppm; MS: *m*/*z* 358 (M$^+$, 75%), 260 (100), 77 (37). Anal. Calcd for C$_{19}$H$_{14}$N$_6$O$_2$: C, 63.68; H, 3.94; N, 23.45. Found: C, 63.87; H, 3.96; N, 23.34.

Synthesis of bis-1,2,3-triazoles 5a,b

To a solution of compound **4** (0.1 g, 0.28 mmol) in toluene (10 mL) was added dimethyl or diethyl acetylenedicarboxylate (1.67 mmol), and the mixture was heated under reflux for 24–48 h. The reaction progress was monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was crystallized from EtOH or purified using PLC on silica gel with *n*-hexane/acetone (1:1) as eluent.

2,6-Bis{4-[(4,5-dimethoxycarbonyl-1,2,3-triazole-1-yl)methyl] phenyl}-4*H*-pyran-4-one (5a): White solid; yield 0.15 g (84%); mp 227–228°C (from EtOH); FT-IR: 3074, 2956, 1739 (ester C=O), 1643 (pyrone C=O), 1554, 1512, 1460, 1386, 1211, 1062, 945, 825 cm^{-1}; ^{1}HNMR (CDCl$_3$) δ: 3.92 (s, 6H, -CH$_3$), 3.98 (s, 6H, -CH$_3$), 5.90 (s, 4H, -CH$_2$-), 6.79 (s, 2H,pyrone-H), 7.44 (d, 4H, *J* = 8.1 Hz, Ar-H),7.82 (d, 4H, *J* = 8.1 Hz, Ar-H) ppm; ^{13}C NMR (CDCl$_3$) δ: 51.9, 52.4, 52.5, 110.9, 125.5, 127.8, 128.3, 130.8, 136.4, 139.6, 157.6, 159.3, 161.4 (ester C=O), 178.8 (pyrone C=O) ppm. Anal. Calcd for C$_{31}$H$_{26}$N$_6$O$_{10}$: C, 57.94; H, 4.08; N, 13.08. Found: C, 58.11; H, 4.15; N, 13.00.

2,6-Bis {4-[(4,5-diethoxycarbonyl-1,2,3-triazole-1-yl)methyl] phenyl}-4*H*-pyran-4-one (5b): This compound was purified by PLC on silica gel using *n*-hexane/acetone (1:1) as eluent; brown oil; yield 0.1 g (51%); FT-IR: 3124, 2958, 2854, 1728 (ester C=O), 1643 (pyrone C=O), 1544, 1535, 1427, 1352, 1234, 1093, 1041, 945, 806 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 1.31 (t, 6H, *J* = 7.1Hz, -CH$_3$), 1.41(t, 6H, *J* = 7.1 Hz, -CH$_3$-), 4.37 (q, 4H, *J* = 7.1 Hz, -CH$_2$-), 4.44 (q, 4H, *J* = 7.1 Hz, -CH$_2$-), 5.89 (s, 4H, -CH$_2$-), 6.79 (s, 2H, pyrone-H), 7.43 (d, 4H, *J* = 8.2 Hz, Ar-H), 7.80 (d, 4H, *J* = 8.2 Hz, Ar-H) ppm; ^{13}C NMR (CDCl$_3$) δ: 12.8, 13.5, 52.2, 61.3, 62.0, 110.9, 125.5, 127.8, 128.4, 130.8, 136.5, 139.9, 157.3, 159.1, 161.5 (ester C=O), 178.8 (pyrone C=O) ppm. Anal. Calcd for C$_{35}$H$_{34}$N$_6$O$_{10}$: C, 60.17; H, 4.90; N, 12.03. Found: C, 59.97; H, 4.95; N, 12.10.

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