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Synthesis of polysubstituted furans via a novel and efficient heterocyclization approach

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Abstract A new catalyst-free, one-pot synthesis of polysubstituted furans is reported. A series of [4-(4-aryl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)-methanones was synthesized via multicomponent reaction of 1,3-di(pyridin-2-yl)propane-1,3-dione, aryl aldehydes, and cyclohexyl isocyanide.

Keywords Polysubstituted furan · Catalyst-free · IMCR

Introduction

Multicomponent reactions (MCRs) include a series of simultaneous multi bond-forming reactions which enable construction of structurally diverse compounds through combinatorial interactions between simple starting materials, leading to the target products by one-pot operation [1, 2]. Simplified purification of products because of incorporation of all the starting substrates into the final product, and the possibility of preparing complex products starting from simple initial substrates in one-step operation, are other advantages of MCRs [3, 4].

Furans are important intermediates for synthesis of oxygenated natural products [6]. Polysubstituted furans are among the most important heterocyclic compounds with widespread occurrence in nature [5, 6]. The pharmacological and biological

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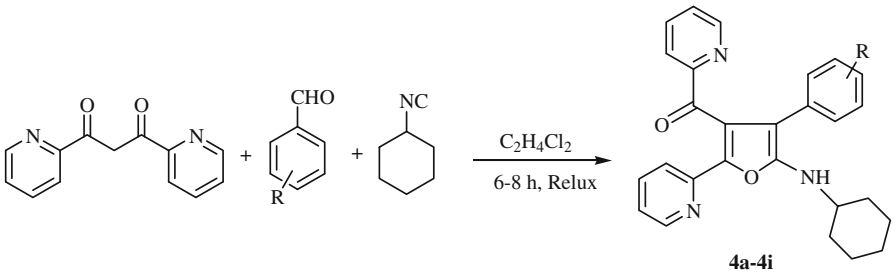
activities of furan derivatives have induced and encouraged a number of research groups to introduce a wide spectrum of synthetic designs with the aim of obtaining pharmacologically and biologically more active heterocyclic compounds [7–9]. Furthermore, many polysubstituted furans have been widely used as important reaction intermediates in the total synthesis and synthetic industry.

Isocyanide-based MCRs (IMCRs), introduced in 1990s by Passerini and Ugi [10–13], have attracted specific attention because of their high efficiency in synthesis of various heterocyclic compounds. Consequently, many efforts have been devoted to development of synthetic methods which allow rapid, efficient, and selective access to the furan motif. Although structurally diverse furan derivatives have been synthesized by applying isocyanide-based MCRs [14–21], to the best of our knowledge, this synthetic plan has not been applied for synthesis of [4-(4-aryl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)methanone derivatives.

As part of our continuing effort on the design of new routes for preparation of heterocyclic compounds [22], in this study, we designed a one-pot synthesis for preparation of fully substituted furans **4a**–**4i** starting from 1,3-di(pyridin-2-yl)propane-1,3-dione, aryl aldehydes, and cyclohexyl isocyanide (Scheme 1).

Results and discussion

Initially, the reaction of cyclohexyl isocyanide, benzaldehyde, and 1,3-di(pyridin-2-yl)-propane-1,3-dione in $C_2H_4Cl_2$ at reflux condition proceeded spontaneously, leading to [5-(cyclohexylamino)-4-phenyl-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)methanone (**4a**) in good yield. The effect of solvent on the mentioned reaction was then investigated



Scheme 1 Multicomponent synthesis of polysubstituted furans

Table 1 Influence of solvent on the catalyst-free reaction of benzaldehyde, 1,3-di(pyridin-2-yl)propane-1,3-dione, and cyclohexyl isocyanide

Solvent	$C_2H_4Cl_2$	EtOH	CH_3CN	CH_2Cl_2	DMF	THF
Yield (%)[a,b]	84	70	78	68	80	55

[a] All reactions carried out at reflux condition for 8 h. Reaction conditions: benzaldehyde (1.0 equiv), 1,3-diketone (1.0 equiv), cyclohexyl isocyanide (1.1 equiv)

[b] Isolated yields

Table 2 Results of multicomponent synthesis of [4-(4-aryl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)methanones

Entry[a]	Ar	Product	Time (h)	Yield (%)[a]
1	C_6H_5	**4a**	6	84
2	4-NO_2–C_6H_4	**4b**	6	90
3	4-Cl–C_6H_4	**4c**	6	90
4	4-Br–C_6H_4	**4d**	6.5	87
5	4-CH_3–C_6H_4	**4e**	7	86
6	4-CH_3O–C_6H_4	**4f**	7	84
7	2-Cl–C_6H_4	**4 g**	8	82
8	2-NO_2–C_6H_4	**4 h**	8	80
9	2-Br–C_6H_4	**4i**	8	80

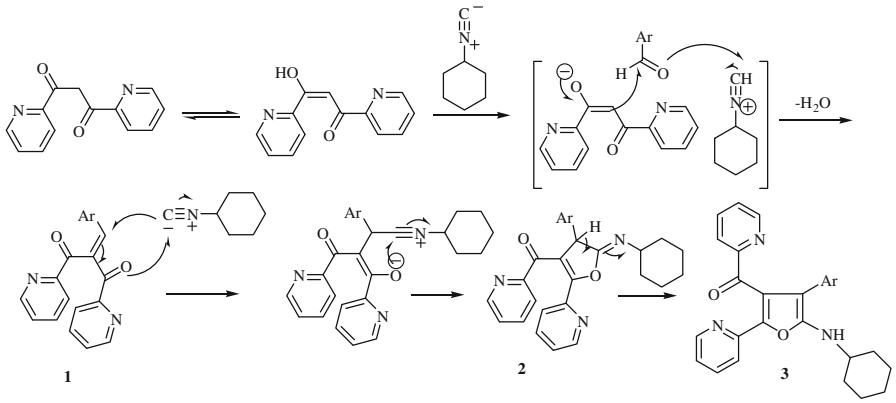
[a] Yield of isolated products

to identify the most appropriate medium for this heterocyclization reaction, with the best results being obtained in $C_2H_4Cl_2$ (Table 1). Therefore, $C_2H_4Cl_2$ was chosen as the solvent for further synthesis. Under these optimized reaction conditions, a series of [4-(4-aryl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)methanone derivatives was synthesized with good yield. The results are summarized in Table 2.

The structure of products was determined on the basis of their elemental analysis, mass spectrometry, nuclear magnetic resonance (NMR), and infrared (IR) spectral data. The elucidation of the structure of **4f** using spectral data is discussed as an example. The ^{1}H NMR spectrum of **4f** consisted of multiplet signals for the cyclohexyl rings (δ_H 1.12–2.15 ppm) and the N–CH resonance (δ_H 3.40) and a sharp singlet for the methoxy group (δ_H 3.65 ppm). A broad resonance (δ_H 5.90 ppm) was observed for the NH group. The aromatic hydrogens give rise to multiplet signals in the aromatic region of the spectrum. Furthermore, the protons next to the nitrogen atom of the pyridine rings are deshielded (δ_H 8.65 and 8.85 ppm) since there is a lower electron density around them. Additionally, the mass spectra of this compound displayed molecular ion peak at 543 *m/z* value. The ^{13}C NMR spectrum of **4f** showed 24 distinct resonances in agreement with the proposed structure. Four signals (δ = 92.1, 111.3, 140.1, and 158.9 ppm) are assigned to the furan carbon atoms. Also, aliphatic carbons could be carefully assigned in the range δ 20.6–52.1 ppm. Moreover, the elemental analysis data were in good accordance with the calculated data.

The scope and limitations of the reaction with respect to the aldehyde component were examined, and the results are presented in Table 2. It was determined that substituted aromatic aldehydes containing electron-withdrawing groups and electron-donating groups tolerate the reaction conditions with good yields.

A reasonable mechanism for the synthesis of polysubstituted furans is depicted in Scheme 2. The mechanism may involve initial formation of a conjugated electron-deficient heterodyne intermediate by Knoevenagel condensation of the 1,3-diketones and the aromatic aldehyde (**1**) followed by a Michael-type addition reaction with cyclohexyl isocyanide to afford an iminolactone **2**, which then isomerizes to furnish the product **3** (Scheme 2). Presumably, the isomerization of **2**



Scheme 2 The proposed mechanism for the catalyst-free synthesis of polysubstituted furans

to **3** is driven by the stability of the fully conjugated aminofuran heteroaromatic moiety.

Conclusions

A novel and catalyst-free synthetic pathway to synthesize a series of [4-(4-aryl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)methanones by one-pot cyclocondensation of 1,3-di(pyridin-2-yl)propane-1,3-dione, aryl aldehydes, and cyclohexyl isocyanide is described.

Experimental

A mixture of an aldehyde (1 mmol), 1,3-diphenylpropane-1,3-dione (1 mmol), and cyclohexyl isocyanide (1.1 mmol) in $C_2H_4Cl_2$ (5 mL) was stirred at reflux condition for appropriate time. The progress of the reactions was monitored by thin-layer chromatography (TLC, ethylacetate:*n*-hexane 1:5). After cooling to room temperature, the resulting precipitate was filtered and chromatographed on silica gel, eluting by ethylacetate:*n*-hexane 1:5 to obtain the desired pure product. The spectral data of the selected products are as follows:

[5-(Cyclohexylamino)-4-phenyl-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)methanone (**4a**) FT-IR (ν_{max}, cm^{-1}): 3335 (N–H), 1655 (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 1.20–2.10 (10H, m, $5CH_2$), 3.44 (1H, m, N–CH), 5.45 (1H, s, NH), 7.25–7.55 (9H, m, Ar), 7.70–8.45 (4H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 21.5, 26.2, 30.5, 52.6, 95.6, 112.8, 124.9, 119.4, 122.6, 125.7, 127.3, 128.0, 128.3, 129.5,129.9, 136.2, 137.1, 139.3, 148.3, 150.9, 155.2, 160.7, 180.5. EIMS (*m*/*z*): 423 (M+). Anal. Calcd. for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92; Found: C, 76.23; H, 5.89; N, 9.87.

[5-(Cyclohexylamino)-4-(4-nitrophenyl)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)-methanone (**4b**) FT-IR (ν_{max}, cm^{-1}): 3325 (N–H), 1650 (C=O), 1320 and 1510 (NO_2); ^1H NMR (250 MHz, $CDCl_3$): δ 1.15–2.15 (10H, m, $5CH_2$), 3.35 (1H, m, N–CH), 5.70 (1H, s, NH), 7.20–7.55 (3H, m, Ar), 7.60–7.95 (4H, m, Ar), 8.05–8.45 (3H, m, Ar), 8.70–8.82 (2H, m, Ar). EIMS (*m*/*z*): 468 (M+). Anal. Calcd. for $C_{27}H_{24}N_4O_4$: C, 69.22; H, 5.16; N, 11.96; Found: C, 68.77; H, 5.11; N, 11.90.

[4-(4-Bromophenyl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)-methanone (**4d**) FT-IR (ν_{max}, cm^{-1}): 3220 (N–H), 1635 (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 1.15–2.20 (10H, m, $5CH_2$), 3.53 (1H, m, N–CH), 6.15 (1H, s, NH), 7.25–7.75 (7H, m, Ar), 7.80–8.25 (3H, m, Ar), 8.60–8.80 (2H, m, Ar). EIMS (*m*/*z*): 501 (M+). Anal. Calcd. for $C_{27}H_{24}BrN_3O_2$: C, 64.55; H, 4.81; N, 8.36; Found: C, 64.13; H, 4.77; N, 8.30.

[5-(Cyclohexylamino)-4-(4-methoxyphenyl)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)methanone (**4f**) FT-IR (ν_{max}, cm^{-1}): 3312 (N–H), 1660 (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 1.12–2.15 (10H, m), 3.40 (1H, m, N–CH), 3.65 (3H, s, OMe), 5.90 (1H, s, NH), 6.90–7.38 (6H, m, Ar), 7.50–7.83 (4H, m, Ar), 8.65 (1H, m, Ar), 8.85 (1H, m, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 20.6, 25.4, 30.1, 52.1, 92.1, 111.3, 118.8, 119.4, 122.6, 124.4, 126.1, 126.9, 128.3, 129.5,129.9, 135.5, 135.9, 140.1, 147.8, 149.1, 153.2, 158.9, 169.8. EIMS (*m*/*z*): 543 (M+). Anal. Calcd. for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.27; Found: C, 74.01; H, 5.93; N, 9.20.

[4-(2-Chlorophenyl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl)-methanone (**4h**) FT-IR (ν_{max}, cm^{-1}): 3335 (N–H), 1657 (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 1.15–2.20 (10H, m), 3.12 (1H, m, N–CH), 4.85 (1H, s, NH), 7.20–7.57 (6H, m, Ar), 7.70–7.85 (3H, m, Ar), 7.90–8.45 (3H, m, Ar). EIMS (*m*/*z*): 457 (M+). Anal. Calcd. for $C_{27}H_{24}ClN_3O_2$: C, 70.81; H, 5.28; N, 9.18; Found: C, 70.22; H, 5.17; N, 9.11.

2-Benzylidene-1,3-di(pyridin-2-yl)propane-1,3-dione [intermediate (**1**)]: ^1H NMR (250 MHz, $CDCl_3$): δ 6.95 (s, 1H), 7.35–7.75 (m, 5H), 7.80–8.25 (m, 5H), 8.85 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.5, 127.5, 128.3, 129.8, 131.5, 134.0, 136.6, 138.1, 148.9, 154.2, 156.5, 188.7. EIMS (*m*/*z*): 314 (M+). Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91; Found: C, 76.24; H, 4.54; N, 8.96.

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