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Isocyanic-based multicomponent synthesis of novel polysubstituted furans in water

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ABSTRACT

An ultrasound assisted, rapid and eco-friendly procedure for the synthesis of new fully substituted furans employing one-pot three-component condensation reaction of 1,3-di (pyridin-2-yl) propane-1,3-dione or 1,3-diphenylpropane-1,3-dione, aryl aldehydes and cyclyhexyl isocyanide has been developed in water.

KEYWORDS

IMCRs;
Multicomponent;
Polysubstituted furan.

INTRODUCTION

Polysubstituted furans are one of the important structural units as well as broadly found in many natural products and pharmaceutical substances[1,2]. Furthermore, many of polysubstituted furans as important reaction intermediates have been widely used in the total synthesis and synthetic industry[3,4]. Therefore, organic chemists have been making extensive efforts to construct furan derivatives by developing new and efficient synthetic methodologies[5-10].

Isocyanide-based multicomponent reactions (IMCRs), such as the Passerini and the Ugi reactions are very useful for the diversity-oriented synthesis of collections of compounds[11]. The outstanding position of IMCRs can be traced back to the exceptional reactivity of the functional group of the isocyanide which reacts with nucleophiles and electrophiles at the same atom, while the other functional groups typically react at different atoms with nucleophiles and electrophiles. Although, structurally diverse furan derivatives have been synthesized applying isocyanide-based MCRs[12-20], to the best of our knowledge, this synthetic plan has not been applied for the synthesis of [4-(4-aryl)-5-(cyclohexylamino)-2-(pyridin-4-yl)furan-3-yl](pyridin-4-yl)methanone and [4-(4-aryl)-5-(cyclohexylamino)-2-phenylfuran-3-yl](phenyl)methanone derivatives.

In the continuation of our general interest in the synthesis of heterocyclic compounds by the MCR reactions[21-25], herein, we wish to report a new three-component methodology for the synthesis of fully substituted furans **(4a-4j)** by a catalyst-free one-pot reaction of 1,3-diphenylpropane-1,3-dione or 1,3-di(pyridin-2-yl)propane-1,3-dione, cyclohexyl isocyanide and aromatic aldehydes (Scheme 1).

EXPERIMENTAL

General procedure for synthesis of polysubstituted furans

Amixture of an aldehyde (1 mmol), 1,3-diketon (1mmol) and cyclohexylisocyanide (1.1 mmol) in water (5 mL) in the presence of tetraethyl ammonium chloride (10 mol%) was stirred at 50 ^{0}C under ultrasonic irradiation using ultrasonic cleaner with a fre-

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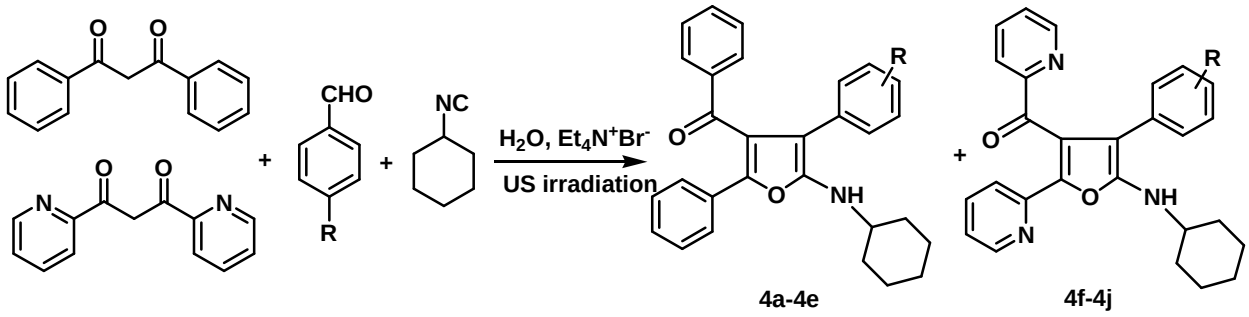


Scheme 1

quency of 40 KHz and a nominal power 100 W for the appropriate time (TABLE 1). The progress of the reactions were monitored by TLC (ethylacetate:*n*-hexanes 1:5). After cooling to room temperature, the resulting precipitate was filtered off and washed with water. The solid was dried and crystallized from CH_3CN:EtOH (1:4) to obtain the pure desired product.

[5-(cyclohexylamino)-2,4-diphenylfuran-3-yl](phenyl)methanone (4a)

FT-IR (ν_{max}, cm^{-1}): 3335 (N-H), 1655 (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 1.30–2.15 (10H, m), 2.90 (1H, m, N-CH), 6.45 (1H, s, NH), 7.10–7.55 (8H, m, Ar), 7.60–7.78 (7H, m, Ar). Anal. Calcd. for $C_{29}H_{27}NO_2$: C, 82.63; H, 6.46; N, 3.32; Found: C, 81.33; H, 6.39; N, 3.27. EIMS (m/z): 421 (M+).

[5-(cyclohexylamino)-4-(4-nitrophenyl)-2-phenylfuran-3-yl](phenyl)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 1.20–2.08 (10H, m), 2.70 (1H, m, N-CH), 6.90 (1H, s, NH), 7.15-7.45 (6H, m, Ar), 7.55–7.95 (8H, m, Ar). Anal. Calcd. for $C_{29}H_{26}N_2O_4$: C, 74.66; H, 5.62; N, 6.00; Found: C, 74.37; H, 5.55; N, 5.93. EIMS (m/z): 466 (M+).

[5-(cyclohexylamino)-2-phenyl-4-p-tolylfuran-3-yl](phenyl)methanone (4d)

FT-IR (ν_{max}, cm^{-1}): 3310 (N-H), 1652 (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 1.25–2.14 (10H, m), 2.75 (1H, m, N-CH), 2.25 (3H, s, Me), 6.24 (1H, s, NH), 7.10-7.55 (10H, m, Ar), 7.55–7.80 (5H, m, Ar). Anal. Calcd. for $C_{30}H_{29}NO_2$: C, 82.73; H, 6.71; N, 3.22; Found: C, 82.21; H, 6.63; N, 3.16. EIMS (m/z): 435 (M+).

[5-(cyclohexylamino)-4-(4-methoxyphenyl)-2-phenylfuran-3-yl](phenyl)methanone (4e)

FT-IR (ν_{max}, cm^{-1}): 3312 (N-H), 1660 (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 1.24–2.10 (10H, m), 2.82 (1H, m, N-CH), 3.62 (3H, s, OMe), 5.90 (1H, s, NH), 6.90–7.42 (8H, m, Ar), 7.55–7.75 (6H, m, Ar). Anal. Calcd. for $C_{30}H_{29}NO_3$: C, 79.80; H, 6.47; N, 3.10; Found: C, 78.55; H, 6.38; N, 3.05. EIMS (m/z): 451 (M+).

[4-(4-bromophenyl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl](pyridin-2-yl) metha anone (4h)

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)met hanone (4j)

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.

2-Benzylidene-1,3-di(pyridin-2-yl)propane-1,3-

dione[1]

^{1}H 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.

RESULTS AND DISCUSSION

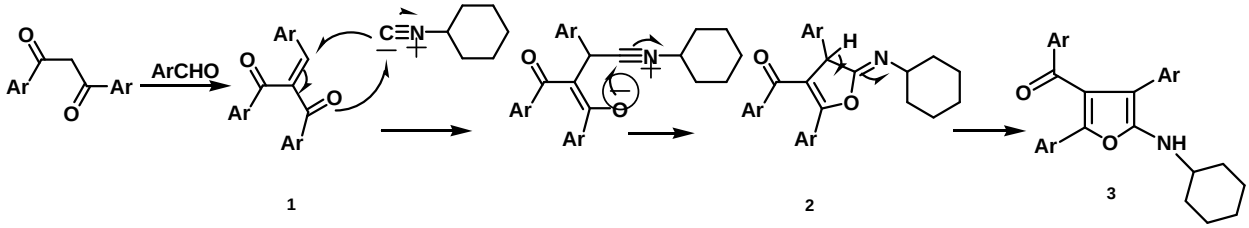
Recently, a great attention has been focused on the use of water as green solvent in organic transformations. Water is a desirable solvent for chemical reactions because it is safe, non-toxic, environmentally friendly, readily available, and inexpensive compared to organic solvents. Since the pioneering studies by Breslow[26,27] on Diels–Alder reactions, there has been an increasing recognition that organic reactions can proceed well in aqueous media offering key advantages over organic solvents such as rate enhancement and insolubility of the final products which facilitates their isolation.

In this study, first a mixture of 1,3-diphenylpropane-1,3-dione, benzaldehyde, and cyclohexyl isocyanide in water was irradiated under sonication for 45 min afforded [5-(cyclohexylamino)-2,4-diphenylfuran-3-yl](phenyl)methanone in good yield (TABLE 1, entry 1). Encouraged by this success, the scope of the reaction with respect to the aldehyde component was examined. As shown in TABLE 1, aromatic aldehydes containing both electron donating and withdrawing groups reacted successfully giving [4-(4-aryl)-5-(cyclohexylamino)-2-phenylfuran-3-yl](phenyl)methanone derivatives **(4a-4e)** in good yields.

Subsequently, the attention was turned to the use of 1,3-di(pyridin-2-yl)propane-1,3-dione, the reaction of which gave the corresponding [4-(4-aryl)-5-(cyclohexylamino)-2-(pyridin-4-yl)furan-3-yl](pyridin-4-yl)methanone derivatives **(4f-4j)** in good to excellent yields (TABLE 1).

The reasonable mechanism may involve the initial formation of a conjugated electron-deficient heterodyne **(1)** by a Knoevenagel condensation of the 1,3-diketones and the aromatic aldehyde followed by a Michael-type addition reaction with cyclohexyl isocyanide to afford the iminolactone **(2)**, which then isomerizes to furnish the **(3)** (Scheme 2). Presumably, the isomerization of **(2)** to **(3)** is driven by the stability of the fully conjugated aminofuran heteroaromatic moiety. To support the proposed mechanism, the intermediate of 2-benzylidene-1,3-di (pyridin-2-yl) propane-1,3-dione was isolated and characterized. The spectra analysis could prove the existence of such intermediate.

The structure of products was determined on the basis of their elemental analyses, mass spectrometry, NMR and IR spectral data. As an example, the elucidation of the structure of **(4j)** using spectral data is discussed. The ^{1}H NMR spectrum of **(4j)** 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. Moreover, the elemental analysis data were in a good accordance with the calculated data. 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



Scheme 2

TABLE 1 : Results of multicomponent synthesis of [4-(4-aryl)-5-(cyclohexylamino)-2-phenylfuran-3-l] (phenyl) methanones (4a-4e) and [4-(4-aryl)-5-(cyclohexylamino)-2-(pyridin-2-yl)furan-3-yl] (pyridin-2-yl) methanones (4f-4j)

Entry[a]	Ar	Product	Time (min)	Yield (%)[a]
1	C_6H_5	4a	45	90
2	4-NO_2-C_6H_4	4b	40	90
3	4-Br-C_6H_4	4c	42	88
4	4-CH_3-C_6H_4	4d	50	86
5	4-CH_3O-C_6H_4	4e	50	85
6	C_6H_5	4f	50	86
7	4-NO_2-C_6H_4	4g	54	90
8	4-Br-C_6H_4	4h	52	84
9	4-CH_3-C_6H_4	4i	55	85
10	4-CH_3O-C_6H_4	4j	60	85

a) Isolated yields

assigned in the range d 20.6–52.1 ppm.

CONCLUSION

In summary, an efficient, green, rapid and ultrasound assisted synthesis of polysubstituted furans via the coupling of cyclohexyl isocyanide, aldehydes, and 1,3-di(pyridin-2-yl)propane-1,3-dione or 1,3-diphenylpropane-1,3-dione is described. This procedure offers significant advantages over other methodologies such as operational simplicity, rapid synthesis, ease of product isolation, cleaner reaction profiles and eco-friendly nature of the solvent.

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