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A Modified and Green Methodology for Preparation of Polysubstituted Furans

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ABSTRACT: *In this study, we introduced a very simple, one-pot and green methodology for preparation of polysubstituted furans by reaction of aromatic aldehydes, DMAD, and alkylisocyanides in water and at room temperature.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:259–262, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20086

INTRODUCTION

Polysubstituted furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products and in important pharmaceuticals, but they can also be employed in synthetic chemistry as building blocks [1,2]. Furans can be, in principle, synthesized from either cyclization of acyclic precursors or derivatization of the furan ring [3,4]. In the latter case, usually the introduction of substituents at the 2- or 5-position is relatively easy, while a similar operation at the 3- or 4-position is difficult. Thus, one of the most pursued entries to polysubstituted furans is the cyclization reaction of acyclic precursors since different substituents can be preloaded at the desired locations in the starting materials [5,6]. Thus, the substituent-incorporation capability of the starting materials will be a key point for the efficiency of the related methodology.

Recently some new methods have been reported for synthesis of densely polysubstituted furans [7–10]. Of the simplest and the most interesting report is the procedure which is based on three-component reaction of alkyl isocyanides, dialkyl acetylendicarboxylates, and aromatic aldehydes [7]. The addition of nucleophilic carbenes such as isocyanides to dimethyl acetylenedicarboxylate (DMAD) has been investigated in detail [11]. Furans with different substituents have been formed from the reaction of initially formed 1:1 zwitter ionic species I (Fig. 1) and aromatic aldehydes [7].

However, in spite of very good improvements in synthesis of furans, development of alternative modifications is essential. In the context of our general interest in the synthesis of heterocyclic compounds by the reaction of dipolar species with carbonyl compounds [12], here we report a new green one-pot three-component methodology for preparation of polysubstituted furans by trapping of zwitterionic intermediate **I** (Fig. 1) with aromatic aldehydes in water as eco-compatible solvent.

RESULTS AND DISCUSSION

Water has all factors of an ideal solvent and so synthetic organic chemistry in water has been widely used in recent years [13]. Moreover, because of high-heat capacity, water provides the best surroundings for product scale-up. As was mentioned, in Introduction, recently Nair and Vinod [7] reported a novel one-pot three-component procedure for preparation

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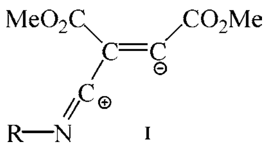


FIGURE 1

of polysubstituted furans using DMAD, alkyl isocyanides, and aromatic aldehydes (Scheme 1, conditions i). Reactions were accomplished in refluxing benzene and completed after 2–8 h, and the products were formed in moderate yields. These authors apparently believed that water prevented the reaction progress, and thus they used dry and deoxygenated benzene as the reaction medium.

We found that water not only has a preventive effect on reaction improvement but also it effectively accelerated the reaction rate. In a typical procedure, to a 1:1 mixture of aromatic aldehyde **1** and dialkyl acetylenedicarboxylate **2** in water, 1 equivalent of alkyl isocyanide **3** was added, and the reaction mixture was allowed to rotate at room temperature for an appropriate time (see Table 1). The pure products **4** were afforded in good to excellent yields with recrystallization from ethanol (for entries **a–f**) or by column chromatography using hexane–ethyl acetate mixture as the eluent (entries **g–j**). The results obtained are summarized in Table 1.

All products **4a–e** are new compounds, and they were characterized unambiguously by their elemental analysis and spectroscopic data (see Experimental section). Their IR spectra showed signals at 3310–3433 cm^{-1} assignable to the NH groups and two strong absorptions at about 1730 and 1660 cm^{-1} assignable to the two ester carbonyls. In the ^1H NMR spectra, the amine protons resonated in the range of δ 6.5–7 and are water exchangeable.

In the ^{13}C NMR spectra the two ester carbonyls resonated at δ 163 and 164. In addition, aliphatic protons and carbons could be carefully assigned at the ranges of δ 1.2–4.0 and 14–81 ppm, respectively. Compounds **4f–j** are known [7] and characterized by comparison of their physical properties and spectroscopic data with those of previously reported.

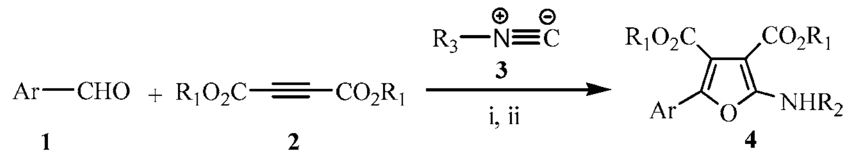
In summery, we have described a very simple, efficient, and green methodology for preparation of polysubstituted furans in water as eco-compatible solvent. The carried out study allows us to obtain furans in good to high yields, using ordinary temperatures, and for relatively low-reaction time.

EXPERIMENTAL

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Bomen FT-IR-MB 100 spectrometer. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as internal standard. Chemical shifts are reported (δ) relative to TMS and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer. Elemental analysis for C, H, and N were performed using a Heraus CHN rapid analyzer. DMAD and isocyanides derivatives were obtained from Merck and Fluka and were used without further purification.

*Synthesis of 2-(Cyclohexylmethyl)-5-(4-nitrophenyl)furan-3,4-dicarboxylic Acid Dimethyl Ester (**4a**) as a General Procedure*

To a magnetically stirred suspension of 4-nitrobenzaldehyde **1a** (0.200 g, 1.32 mmol) and DMAD **2a** (0.207 g, 1.45 mmol) in water (40 mL), cyclohexyl isocyanide **3a** (0.159 g, 1.45 mmol) was added and the reaction mixture was stirred at room temperature for 1.5 h. After filtration, the crude product was recrystallized from ethanol to give pure **4a** as light-yellow solid. Yield 95%, mp 169–171°C. IR (KBr) υ: 3433 (NH), 1726 and 1674 (2C=O), 1325, 1223, 1104 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28–2.10 (m, 11H, cyclohexyl), 3.80–3.98 (broad s, 7H, CH-N and $2CO_2CH_3$), 6.74 (s, 1H, NH), 7.62 (d, $J = 8.90$, 2H), 8.22 (d, $J = 8.92$, 2H). ^{13}C NMR ($CDCl_3$) δ: 24.48, 25.33, 33.35, 51.38, 51.72, 52.96, 88.80, 117.84, 123.93, 124.26, 134.94, 137.89, 145.90, 161.54, 164.36, 165.35. MS m/z (%): 402 (100), 371 (20), 320 (45), 288 (99), 256 (30), 151 (80), 55 (90). Anal.



i: dry benzene, reflux, 2-8 hr [7]
ii:H_2O, r.t., 1.5-5 hr (our modified procedure)

SCHEME 1

TABLE 1 Reaction Time and Yields of Furans **4**

4	*Ar*	*R_1*	*R_2*	*Time (h)*	*Yield^a*
a	4-Nitrophenyl	Me	Cyclohexyl	1.5	95
b	4-Nitrophenyl	Me	*t*-Bu	1.5	92
c	4-Nitrophenyl	*t*-Bu	Cyclohexyl	1.5	88
d	4-Nitrophenyl	*t*-Bu	*t*-Bu	2	90
e	4-Nitrophenyl	Et	*t*-Bu	1.5	73
f	3-Nitrophenyl	Me	Cyclohexyl	2	93
g	Phenyl	Me	Cyclohexyl	4	84
h	3-Chlorophenyl	Me	Cyclohexyl	3	88
i	4-Chlorophenyl	Me	Cyclohexyl	4	87
j	4-Tolyl	Me	Cyclohexyl	5	91

^{a}Related to isolated yields.

Calcd for $C_{20}H_{22}N_2O_7$ (402): C, 59.70; H, 5.51; N, 6.96. Found: C, 59.64; H, 5.23; N, 7.05.

For viscous liquid products **4g–j**, after completion of the reaction, crude products were extracted with dichloromethane (3 × 15 mL). The organic solvent was evaporated, and the final purification was carried out by column chromatography using a 8.5:1.5 hexane–ethyl acetate mixture.

*2-tert-Butylamino-5-(4-nitro-phenyl)-furan-3,4-dicarboxylic Acid Dimethyl Ester (***4b***).* Light-orange solid; yield 92%, mp 168–170°C, IR (KBr) υ: 3330 (NH), 1730 and 1672 (2 CO_2CH_3), 1609, 1324, 1210 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.53 (s, 9H, $(CH_3)_3$—N), 3.8 (s, 3H, CO_2CH_3), 3.97 (s, 3H, CH_3O_2C), 6.98 (s, 1H, NH), 7.62 (d, $J = 8.79$, 2H), 8.23 (d, $J = 8.72$, 2H). ^{13}C NMR ($CDCl_3$) δ: 29.69, 51.31, 52.95, 53.05, 89.62, 117.48, 123.82, 124.29, 134.86, 138.24, 145.85, 161.81, 164.42, 165.38. MS *m/z* (%): 376 (100), 320 (90), 288 (82), 151 (78), 57 (98). Anal. Calcd for $C_{18}H_{20}N_2O_7$ (376.13): C, 57.44; H, 5.36; N, 7.44. Found: C, 57.53; H, 5.20; N, 7.37.

*2-Cyclohexylamino-5-(4-nitro-phenyl)-furan-3,4-dicarboxylic Acid Di-tert-butyl Ester (***4c***).* Orange solid; yield 88%, mp 178–180°C. IR (KBr) υ: 3410 (NH), 1731, and 1703 (2 CO_2Bu-t), 1614, 1476 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.56 (s, 9H, *t*-Bu), 1.6 (s, 9H, *t*-Bu), 1.33–2.32 (m, 10H, cyclohexyl), 3.72 (d, 1H, CH—N), 6.73 (s, 1H, NH), 7.63 (d, $J = 8.82$, 2H), 8.21 (d, $J = 8.80$, 2H). ^{13}C NMR ($CDCl_3$) δ: 24.52, 25.40, 28.15, 28.66, 33.47, 51.54, 81.05, 82.99, 90.33, 120.09, 124.4, 124.1, 135.52, 137.39, 145.63, 161.34, 163.48, 163.61. 486 (98), 430 (25), 374 (100), 357 (30), 292 (42), 274 (75), 57 (99). Anal. Calcd for $C_{26}H_{34}N_2O_7$ (486.24), C, 64.18; H, 7.04; N, 5.76. Found: C, 64.12; H, 7.134; N, 5.66.

*2-tert-Butylamino-5-(4-nitro-phenyl)-furan-3,4-dicarboxylic Acid Di-tert-butyl Ester (***4d***).* Orange solid; yield 90%, mp 159–162°C, IR (KBr) υ: 3380 (NH), 3075 (CH), 1708 and 1680 (2 CO_2Bu-t), 1609, 1420 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H, CO_2Bu-t), 1.56 (s, 9H, CO_2Bu-t), 1.62 (s, 9H, CO_2Bu-t), 7.28 (s, 1H, NH), 7.64 (d, $J = 9.00$, 2H), 8.22 (d, $J = 9.00$, 2H). ^{13}C NMR ($CDCl_3$) δ: 28.15, 28.63, 29.81, 52.76, 81.13, 83.04, 91.11, 119.78, 123.98, 124.15, 135.50, 137.79, 145.61, 161.55, 163.57, 163.62. Anal. Calcd for $C_{24}H_{32}N_2O_7$ (460.21): C, 62.59; H, 7.00; N, 6.08. Found: C, 62.41; H, 7.09; N, 6.15.

*2-tert-Butylamino-5-(4-nitro-phenyl)-furan-3,4-dicarboxylic Acid Diethyl Ester (***4e***).* Yellow-orange solid; yield 73%, mp 117–119°C, IR (KBr) υ: 3335 (NH), 1720, and 1668 (2 CO_2Et), 1590, 1325 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, $J = 6.00$, 3H, CH_3), 1.41 (t, $J = 6.00$, 2H, CH_3), 1.53 (s, 9H, *t*-But), 4.26 (q, $J = 6.00$, 2H, OCH_2Me), 4.43 (q, $J = 6.00$, 2H, OCH_2Me), 7.02 (s, 1H, NH), 7.61 (d, $J = 9.00$, 2H), 8.22 (d, $J = 9.00$, 2H). ^{13}C NMR ($CDCl_3$) δ: 14.03, 14.33, 29.75, 53.01, 60.18, 62.13, 89.78, 117.98, 123.71, 124.34, 135.07, 137.96, 145.80, 161.89, 164.21, 165.01. Anal. Calcd for $C_{20}H_{24}N_2O_7$ (404.16): C, 59.40; H, 5.98; N, 6.93. Found: C, 59.33; H, 5.79; N, 6.86.

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