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A novel three-component reaction of a secondary amine and a 2-hydroxybenzaldehyde derivative with an isocyanide in the presence of silica gel: an efficient one-pot synthesis of benzo[*b*]furan derivatives

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ABSTRACT

Reaction of an isocyanide with an iminium ion intermediate, formed by reaction between an electron-poor 2-hydroxybenzaldehyde derivative and a secondary amine in the presence of silica gel proceeds smoothly at room temperature to afford benzo[*b*]furan derivatives in high yields.

1. Introduction

Multi-component reactions (MCRs) have attracted significant attention in combinatorial chemistry.[1] Of pivotal importance in this area are the isocyanide-based MCRs such as the versatile Ugi and Passerini reactions.[1–4] The ability of isonitriles to undergo facile addition with a nucleophile and an electrophile under mild conditions makes them useful reactants for the development of novel MCRs.[2,5] Isocyanides,[6] regarded for many years as compounds with unpleasant odor and very few chemical and pharmaceutical applications, are now looked upon as useful synthons with interesting chemical properties. This change in attitude can be attributed primarily to the renaissance of isocyanide-based multi-component reactions (MCRs),[7,8] for example, the Passerini three-component reaction (P-3CR),[9,10] and more importantly, the Ugi four-component reaction (U-4CR),[11,12] with its ability to deliver a wide variety[13] of peptide analogs and heterocyclic compounds for investigation in drug discovery programs.

The well-known Ugi four-component condensation between aldehydes, isocyanides, and ammonium formate affords N-substituted 2-formylaminocarboxamides.[14,15] The reaction between salicylaldehyde, isocyanides, and ammonium formate under Ugi four-component condensation conditions affords benzo[*b*]furan derivatives in low yields.[16]

Furan derivatives, obtained from both synthetic and natural sources, have attracted much interest due to their wide ranging pharmaceutical applications.[17–19] Many naturally occurring furans show interesting biological activities, such as cytotoxic and antitumor properties,[19,20] as well as antispasmodic,[21] antimicrobial,[22,23] and several other potentially useful activities.[24]

2. Results and discussion

As part of our ongoing program to develop efficient and robust methods for the preparation of heterocyclic compounds,[25–30] we report here a simple, one-pot, three-component reaction between isocyanides **4**, secondary amines **1**, and an electron-poor 2-hydroxybenzaldehyde derivative **2** in the presence of silica gel at ambient temperature, leading to benzo[*b*]furan derivatives **7** (Scheme 1 and Table 1). In the absence of silica gel, the yields were only ca. 20% at room temperature after 24 h and in each case several by-products were observed (based on TLC investigations). We also used 2-hydroxybenzaldehyde and 2,5-dihydroxybenzaldehyde in this reaction, but the yields of the corresponding products

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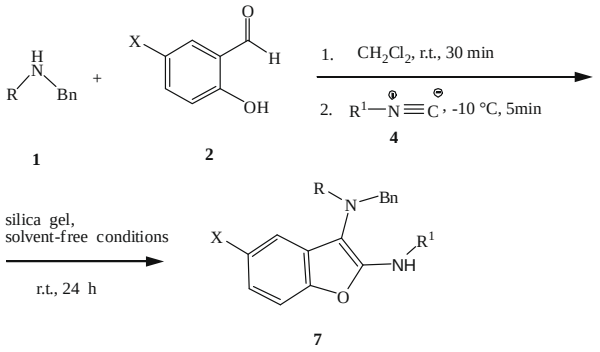
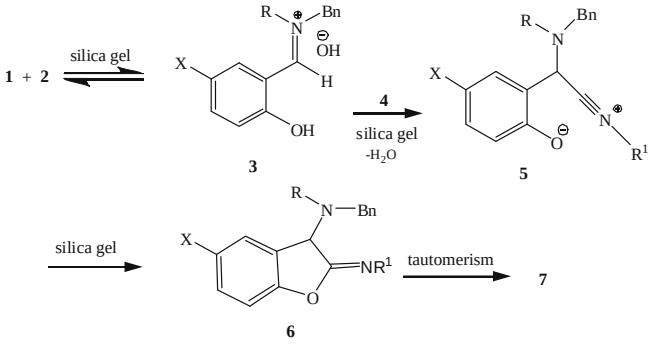


Scheme 1. Three-component synthesis of benzo[*b*]furan derivatives **7** in the presence of silica gel.



Scheme 2. Proposed mechanism for the formation of benzo[*b*]furan derivatives **7** in the presence of silica gel.

7 were very low and in both cases several by-products were observed (based on TLC). As indicated in Table 1, the reactions proceeded efficiently with electron-withdrawing 2-hydroxybenzaldehyde derivatives **2** in the presence of silica gel; electron-releasing 2-hydroxybenzaldehyde derivatives are not suitable starting materials in these reactions. The high yields of **7a–j** can be explained by the greater electrophilicity of carbonyl groups of electron-withdrawing 2-hydroxybenzaldehyde derivatives relative to carbonyl groups of electron-releasing 2-hydroxybenzaldehyde derivatives.

The structures of compounds **7a–j** were deduced from their IR, and high-field ^{1}H and ^{13}C NMR spectra, and their mass spectra. For example, the IR spectrum of **7a** showed a strong absorption at 3415 cm^{-1} indicating the presence of an amine. The ^{1}H NMR spectrum of **7a** consisted of one singlet for the methyl groups (CMe_3, δ = 1.12), one singlet for the two methylenes (2 CH_2 of two benzyls, δ = 4.21), an amine hydrogen atom (δ = 4.07) which was exchangeable with D_2O, a multiplet for the aromatic protons (δ = 7.21–7.37), one doublet of doublets for the aromatic benzo[*b*]furan (C-4(H)) proton (δ = 7.91, $^3J_{HH}$ = 6.5 Hz, $^4J_{HH}$ = 2.3 Hz), and a doublet for the aromatic benzo[*b*]furan (C-6(H)) proton (δ = 8.16, $^4J_{HH}$ = 2.3 Hz). The ^{1}H decoupled ^{13}C NMR spectrum of **7a** showed 15 distinct resonances, the partial assignment of these resonances is given below. The ^{1}H and ^{13}C NMR spectra of compounds **7b–j** were similar to those of **7a**, except for the aromatic moieties and the alkyl groups which exhibited characteristic signals with appropriate chemical shifts.

Although we have not established the mechanism of the reaction in an experimental manner, a plausible reaction sequence that accounts for the formation of **7** is shown in Scheme 2. Thus condensation of 2-hydroxybenzaldehyde derivative **2** and secondary amine **1** would give the iminium ion intermediate **3**, which would react with the alkyl isocyanide **4** to afford intermediate **5**. The ionic intermediate **5** would cyclize into benzofuran **6**. Tautomerization of **6** could then lead to formation of the benzo[*b*]furan derivatives **7**.

Table 1
Synthesis of benzo[*b*]furan derivatives in the presence of silica gel

Product	R^1	R	X[a]	% Yield[b]
7a	*tert*-Butyl	Benzyl	NO_2	90
7b	Cyclohexyl	Benzyl	NO_2	86
7c	1,1,3,3-Tetramethylbutyl	Benzyl	NO_2	94
7d	2,6-Dimethylphenyl	Benzyl	NO_2	91
7e	Benzyl	Benzyl	NO_2	80
7f	*tert*-Butyl	Methyl	NO_2	84
7g	1,1,3,3-Tetramethylbutyl	Methyl	NO_2	90
7h	*tert*-Butyl	Benzyl	Br	85
7i	1,1,3,3-Tetramethylbutyl	Benzyl	Br	88
7j	Cyclohexyl	Benzyl	Br	80

[a] We also used 2-hydroxybenzaldehyde and 2,5-dihydroxybenzaldehyde in this reaction, but the yields of the corresponding products **7** were very low and in both cases several by-products were observed.
[b] Isolated yields.

3. Conclusions

In conclusion, we have developed an efficient route for the one-pot synthesis of benzo[*b*]furan derivatives **7** from simple and readily available isocyanides **4**, secondary amines **1**, and electron-poor salicylaldehydes **2** in the presence of silica gel. The ease of work-up and high yields of products make this procedure a useful addition to modern synthetic methods.

4. General Procedure

Compounds **7a–j**; general procedure exemplified for **7a**: A mixture of dibenzylamine (0.19 mL, 1 mmol) and 2-hydroxy-5-nitrobenzaldehyde (0.167 g, 1 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 0.5 h. To this mixture, a solution of *tert*-butyl isocyanide (0.12 mL, 1 mmol) in dry CH_2Cl_2 (2 mL) at −10 °C was added rapidly and the solution was stirred for 5 min at −10 °C. Subsequently, powdered silica gel (1 g) (Merck) was added rapidly to the reaction mixture which was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was allowed to stand for 24 h at room temperature. Flash column chromatography of the residue using petroleum ether-diethyl ether (10:1) as eluent, gave **7a** as a red viscous oil.

N,N-dibenzyl-N-[2-(tert-butylamino)-5-nitro-1-benzofuran-3-yl]amine, **7a**: Red viscous oil; yield: 90%. IR (KBr) (υ_{max}, cm^{-1}): 3415 (NH), 1646, 1523, 1453, 1346, 1215. ^{1}H NMR (250 MHz, $CDCl_3$) δ_H: 1.12 (9H, s, CMe_3), 4.21 (4H, s, 2 CH_2), 4.07 (1H, br s, NH, exchanged by D_2O addition), 7.21–7.37 (11H, m, H–Ar), 7.91 (1H, dd, $^3J_{HH}$ = 6.5 Hz, $^4J_{HH}$ = 2.3 Hz, H-4, benzofuran), 8.16 (1H, d, $^4J_{HH}$ = 2.3 Hz, H-6, benzofuran). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ_C: 29.93 (3 CH_3 of CMe_3), 52.45 (C of CMe_3NH), 58.73 (2 CH_2), 110.03, 111.89, 128.50 (3 CH, benzofuran), 104.68, 115.30, 152.07, 158.35 (4 C, benzofuran), 143.90 (C(NO_2)), 127.37, 128.38, 129.16 (10 CH), 139.00 (2 C_{ipso}). Anal. Calcd for $C_{26}H_{27}N_3O_3$: C, 72.71; H, 6.34; N, 9.78. Found: C, 72.69; H, 6.32; N, 9.75. MS (EI): *m*/*z* (%) = 429 (M^+, 5), 338 (8), 282 (16), 106 (28), 91 (100), 57 (17), 41 (8).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.115.

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