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Isocyanide-based three-component synthesis of 5-alkylimino-2,5-dihydrofuran-3,4-dicarboxylate derivatives

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Abstract: The zwitter ion formed from an alkyl isocyanide and dialkyl acetylenedicarboxylate reacts with Phenacyl bromide or its derivatives to form 5-alkylimino-2,5-dihydrofuran-3,4-dicarboxylate in relatively good yields at room temperature under solventless conditions.

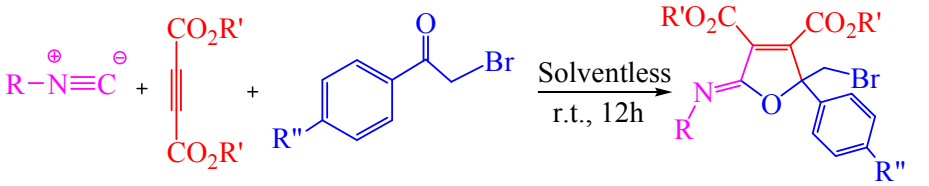
Keywords: Multicomponent reaction; Isocyanide; 5-Alkylimino-2,5-dihydrofuran-3,4-dicarboxylate derivatives; Dialkyl acetylenedicarboxylates.

Introduction

Furans and their derivatives play an important role in organic chemistry due to their presence as key structural units in many natural products and pharmaceuticals, and as essential building blocks for the total synthesis of complex naturally occurring metabolites. Furthermore, poly functionalized furans are versatile synthetic starting materials for the preparation of a variety of heterocyclic and acyclic compounds [1-9], and especially 2,5-disubstituted furan-3,4-dicarboxylates which are very important starting materials in the synthesis of natural products containing tetrahydrofuran rings [10]. For these reasons, the development of new and efficient methods for the synthesis of furan derivatives remains an area of current interest.

As part of our research on the development of new synthetic methods in heterocyclic chemistry [11,12], herein, we describe an efficient synthesis of 5-alkylimino-2,5-dihydrofuran-3,4-dicarboxylate **4** *via* the reaction of an isocyanide **1** with a dialkyl acetylenedicarboxylate **2** and phenacyl bromide or its derivatives **3** at ambient temperature (Scheme 1).

Scheme 1. Synthesis of 5-alkylimino-2,5-dihydrofuran-3,4-dicarboxylate .



1 **2** **3** **4a-e** (82-92%)

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Table 1: Synthesis of 5-alkylimino-2,5-dihydro-3,4-furandicarboxylates

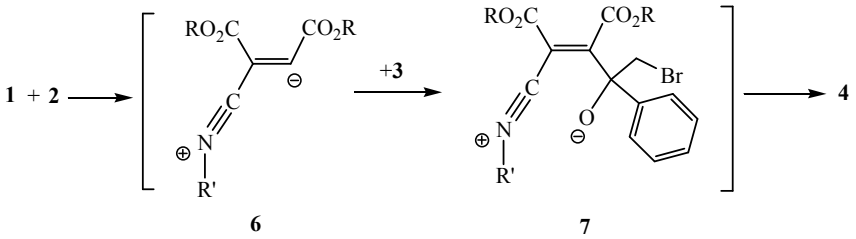
Entry	R	R′	R″	Product	Yield of 4/5 (%)
1	*tert*-Butyl	Me	Me	4a	85/82
2	*tert*-Butyl	Et	Me	4b	84/80
3	*tert*-Butyl	Me	NO_2	4c	85/82
4	Cyclohexyl	Me	OMe	4d	90/87
5	Cyclohexyl	Et	OMe	4e	92/85

Result and discussion

As indicated in Scheme 1, the 1:1:1 addition reaction of isocyanides **1** with dialkyl acetylenedicarboxylates **2** and phenacyl bromide or its derivatives **3** occurs smoothly at room temperature to produce 5-alkylimino-2,5-dihydrofuran-3,4-dicarboxylate **4**. The structures of the products were deduced from their IR, mass, ^{1}H NMR, ^{13}C NMR spectra and C, H, N analysis. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed a singlet at δ = 1.39 for *tert*-butyl group and a singlet at 2.36 for the methyl group. The methylene protons of CH_2Br are diastereotopic and showed characteristic AB quartet systems at δ = 4.12 and 4.52. Two peaks at δ = 160.9, and 162.3 are observed in the ^{13}C NMR spectrum of **4a**, which are attributed to the carbonyl groups. The ^{1}H and ^{13}CNMR spectra of **4b–4e** are similar to those for **4a** except for the imino or aromatic moieties and the substituents in position 4, which show characteristic resonances in appropriate regions of the spectrum.

To explore the scope of this reaction further, we extended our studies to the reaction of various dialkyl acetylenedicarboxylates and isocyanides with phenacyl bromide. As indicated in Table 1, the reactions proceeded very efficiently in excellent yields. Although the mechanism of this reaction has not been established, a plausible rationalization can be advanced to explain product formation (Scheme 2).

Scheme 2. Proposed mechanism for the synthesis of 5-alkylimino-2,5-dihydrofuran-3,4-dicarboxylate.



On the basis of the well-established chemistry of isocyanides, it is reasonable to assume that zwitterionic intermediate **6** produced by reaction between the isocyanide and the dialkyl acetylenedicarboxylate adds to phenacyl bromide **3** resulting in the formation of **7**, which undergoes cyclization to give the 5-alkylimino-2,5-dihydrofuran-3,4-dicarboxylate **4**.

In conclusion, a convenient, one-pot, three-component method for the synthesis of 5-alkylimino-2,5-dihydrofuran-3,4-dicarboxylate derivatives from readily accessible precursors has been developed. These compounds are important starting materials in the synthesis of natural products containing tetrahydrofuran rings. The present procedure has advantages such as

good functional group tolerance and neutral reaction conditions.

Material and methods

Acetylenic ester, Phenacyl bromide or its derivatives and isocyanides were obtained from *Fluka* and were used without further purification. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H-, and ^{13}C-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; □ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer.

General procedure for the preparation of compounds **4a-e**

A mixture of Phenacyl bromide or its derivatives (2 mmol) and dialkyl acetylenedicarboxylate (2 mmol) was stirred at room temperature. To this mixture, isocyanides (2 mmol) was added slowly. The reaction mixture was stirred for 12 h at room temperature and purified by short column chromatography (silica gel) using petroleum ether-ethyl acetate as eluent. The product was then crystallized from hexane to give the desired compound.

Dimethyl 2-bromomethyl-5-(tert-butylimino)-2-(4-methylphenyl)-2,5-dihydrofuran-3,4-dicarboxylate (4a)

Yellow crystals, yield: 0.74 g (85%), m.p. 121-123 °C. IR (KBr) (ν_{max}/cm^{-1}): 1726, 1680, 1652, 1583, 1263 cm^{-1}. ^{1}H NMR: δ = 1.39 (9 H, s, *Me*$_3$C), 2.36 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.90 (3 H, s, MeO), 4.12 (1 H, d, ^2J = 11.0 Hz, CH), 4.52 (1 H, d, ^2J = 11.0 Hz, CH), 7.16 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.33 (2 H, d, ^3J = 7.5 Hz, 2 CH). ^{13}C NMR: δ = 20.9 (Me), 29.5 (*Me*$_3$C), 36.8 (CH_2Br), 52.7 (MeO), 52.8 (MeO), 54.8 (Me$_3$*C*), 90.5 (C), 125.6 (2 CH), 129.4 (2 CH), 133.8 (C), 138.6 (C), 138.9 (C), 141.9 (C), 152.2 (C=N), 161.0 (C=O), 162.3 (C=O). Anal. Calcd for $C_{20}H_{24}BrNO_5$: C, 54.81; H, 5.52; N, 3.20. Found: C, 54.97; H, 5.74; N, 3.02.

Diethyl 2-bromomethyl-5-(tert-butylimino)-2-(4-methylphenyl)-2,5-dihydrofuran-3,4-dicarboxylate (4b)

Yellow crystals, yield: 0.78 g (84%), m.p. 126-128 °C. IR (KBr) (ν_{max}/cm^{-1}): 1725, 1678, 1662, 1580, 1260 cm^{-1}. ^{1}H NMR: δ = 1.15 (3 H, t, ^3J = 7.3 Hz, Me), 1.27 (3 H, t, ^3J = 7.2 Hz, Me), 1.35 (9 H, s, *Me*$_3$C), 2.34 (3 H, s, Me), 4.10 (1 H, d, ^2J = 11.2 Hz, CH), 4.25-4.30 (2 H, m, OCH_2), 4.32-4.40 (2 H, m, OCH_2), 4.45 (1 H, d, ^2J = 11.2 Hz, CH), 7.15 (2 H, d, ^3J = 7.5 Hz, 2 CH), 7.37 (2 H, d, ^3J = 7.8 Hz, 2 CH). ^{13}C NMR: δ = 13.5 (Me), 14.0 (Me), 21.2 (Me), 29.5 (*Me*$_3$C), 37.4 (CH_2Br), 56.2 (Me$_3$*C*), 60.37 (OCH_2), 61.5 (OCH_2), 87.5 (C), 125.2 (2 CH), 128.9 (2 CH), 133.7 (C), 139.0 (C), 139.5 (C), 142.0 (C), 154.2 (C=N), 162.0 (C=O), 162.8 (C=O). Anal. Calcd for $C_{22}H_{28}BrNO_5$: C, 56.66; H, 6.05; N, 3.00. Found: C, 56.38; H, 5.74; N, 3.30.

Dimethyl 2-bromomethyl-5-(tert-butylimino)-2-(4-nitrophenyl)-2,5-dihydrofuran-3,4-dicarboxylate (4c)

Yellow powder, yield: 0.80 g (85%), m.p. 157-159 °C. IR (KBr) (ν_{max}/cm^{-1}): 1740, 1681, 1658, 1587, 1254 cm^{-1}. ^{1}H NMR: δ = 1.39 (9 H, s, *Me*$_3$C), 3.79 (3 H, s, MeO), 3.90 (3 H, s, MeO), 4.16 (1 H, d, ^2J = 11.2 Hz, CH), 4.44 (1 H, d, ^2J = 11.2 Hz, CH), 7.68 (2 H, d, ^3J = 8.5 Hz, 2 CH), 8.23 (2 H, d, ^3J = 8.5 Hz, 2 CH). ^{13}C NMR: δ = 29.5 (*Me*$_3$C), 35.8 (CH_2Br), 53.1 (MeO), 53.4 (MeO), 55.2 (Me$_3$*C*), 89.9 (C), 123.8 (2 CH), 127.4 (2 CH), 139.5 (C), 140.6 (C), 143.7 (C), 148.0 (C), 151.0 (C=N), 160.7 (C=O), 161.9 (C=O). Anal. Calcd for $C_{19}H_{21}BrN_2O_5$ (469.29): C, 48.63; H, 4.51; N, 5.97. Found: C, 48.80; H, 4.32; N, 5.75.

Dimethyl 2-bromomethyl-5-(cyclohexylimino)-2-(4-methoxyphenyl)-2,5-dihydrofuran-3,4-dicarboxylate (4d)

Pale yellow crystals, yield: 0.86 g (90%), m.p. 137-139 °C. IR (KBr) (ν_{max}/cm^{-1}): 1726, 1680, 1652, 1583, 1263 cm^{-1}. ^{1}H NMR: δ = 1.22-1.88 (10 H, m, 5 CH_2), 2.35 (3 H, s, Me), 3.72 (1 H, m, CH), 3.79 (3 H, s, MeO), 3.81 (3 H, s, MeO), 3.92 (3 H, s, MeO), 4.10 (1 H, d, ^2J = 11.0 Hz, CH), 4.51 (1 H, d, ^2J = 11.0 Hz, CH), 6.90 (2 H, d, ^3J = 8.7 Hz, 2 CH), 7.34 (2 H, d, ^3J = 8.7 Hz, 2 CH). ^{13}C NMR: δ = 24.8 (2 CH_2), 25.6 (CH_2), 32.8 (2 CH_2), 36.7 (CH_2Br), 52.7 (MeO), 52.9 (MeO), 53.1 (MeO), 56.8 (C-N), 86.5 (C), 114.2 (2 CH), 127.0 (2 CH), 134.6 (C), 138.2 (C), 140.3 (C), 148.9 (C), 156.0 (C=N), 160.9 (C=O), 162.0 (C=O). Anal. Calcd for $C_{22}H_{26}BrNO_6$: C, 55.01; H, 5.46; N, 2.92. Found: C, 54.72; H, 5.24; N, 2.70.

Diethyl 2-bromomethyl-5-(cyclohexylimino)-2-(4-methoxyphenyl)-2,5-dihydrofuran-3,4-dicarboxylate (4e)

Yellow crystals, yield: 0.93 g (92%), m.p. 152-154 °C. IR (KBr) (ν_{max}/cm^{-1}): 1734, 1678, 1664, 1580, 1272 cm^{-1}. ^{1}H NMR: δ = 1.25 (3 H, t, ^3J = 7.4 Hz, Me), 1.35 (3 H, t, ^3J = 7.3 Hz, Me), 1.45-1.95 (10 H, m, 5 CH_2), 3.77 (1 H, m, CH), 3.85 (3 H, s, MeO), 4.14 (1 H, d, ^2J = 11.2 Hz, CH), 4.25-4.30 (2 H, m, OCH_2), 4.34 (2 H, q, ^3J =

7.4 Hz, OCH_2), 4.55 (1 H, d, ^2J = 11.2 Hz, CH), 7.12 (2 H, d, ^3J = 8.5 Hz, 2 CH), 7.32 (2 H, d, ^3J = 8.5 Hz, 2 CH). ^{13}C NMR: δ = 13.0 (Me), 14.2 (Me), 24.5 (2 CH_2), 25.4 (CH_2), 33.0 (2 CH_2), 37.3 (CH_2Br), 53.4 (MeO), 57.8 (C-N), 62.4 (OCH_2), 62.9 (OCH_2), 90.4 (C), 113.2 (2 CH), 127.3 (2 CH), 135.2 (C), 137.8 (C), 141.3 (C), 149.0 (C), 156.4 (C=N), 161.6 (C=O), 162.4 (C=O). Anal. Calcd for $C_{24}H_{30}BrNO_6$: C, 56.70; H, 5.95; N, 2.76. Found: C, 56.85; H, 6.12; N, 2.93.

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