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Synthesis of fully substituted iminolactones *via* a three-component condensation of isocyanides and acetylenic esters with 2-bromo-1-(4-bromophenyl)ethanone

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Abstract A novel three-component condensation reaction between an isocyanide, an electron-deficient acetylenic ester, and 2-bromo-1-(4-bromophenyl)-ethanone efficiently provides fully substituted iminolactones in a one-pot condensation reaction without any activation or modification in high yields.

Keywords Multi-component reaction; Isocyanide; Iminolactones; Acetylenic ester.

Introduction

Multi-component reactions (MCRs), due to their productivity, simple procedures, convergence, and facile execution, are one of the best tools in combinatorial chemistry [1]. Therefore, the design of novel MCRs has attracted great attention from research groups working in areas such as drug discovery, organic synthesis, and materials science. As a result, the number of new MCRs has grown rapidly [2].

Recently, iminolactones have been the subject of great consideration because of their effects as antibacterial agents, aldosterone inhibitors, and proper precursors for the preparation of a wide spectrum of natural compounds [3]. Iminolactones could be hydrolyzed with aqueous hydrochloric acid to produce butenolides [4], they are an important class of natural products that are biologically active compounds which is used in medicine and agriculture [5].

So far, many synthetic protocols for the synthesis of iminolactones have been reported [6–12]. The most widely used approach to iminolactones synthesis is the isocyanide based reactions [6–10]. As early as 1982, *Saegusa* and his co-workers reported on the Et_2AlCl-mediated reaction of α,β-unsaturated carbonyl compounds with methyl isocyanide leading to unsaturated *N*-substituted iminolactones, which can be easily converted to γ-butyrolactone [6]. Recently, *Chatani et al.* reexamined a catalytic $[1+4]$ cycloaddition reaction of isocyanides and α,β-unsaturated carbonyl compounds in the presence of a catalytic amount of $GaCl_3$ leading to the formation of unsaturated iminolactone derivatives [9]. Moreover, $GaCl_3$ catalyses the double insertion of aryl isocyanides into terminal and disubstituted epoxides leads to α,β-unsaturated α-amino iminolactones [10]. Furthermore, the reaction of 4,4-disubstituted 2,3-allenamides and organic iodides in toluene afforded iminolactones [11]. Finally, the haloiminolactonization of 4,4-disubstituted 2,3-alkadienamides with copper(II) halide (chloride or bromide) or I_2 in *THF* also proceeded to produce unsaturated iminolactones [12].

As part of an ongoing development of efficient protocols for the preparation of biologically active

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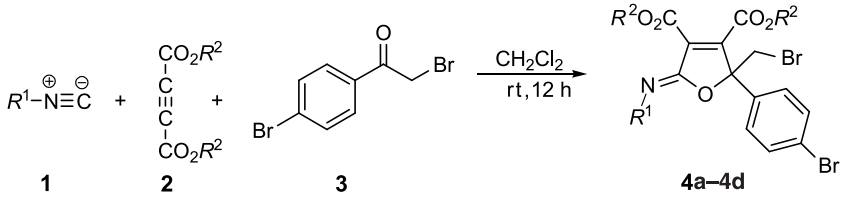


	R^1	R^2	Yield/%
4a	Cyclohexyl	*Me*	97
4b	Cyclohexyl	*Et*	83
4c	*t*-Butyl	*Me*	90
4d	*t*-Butyl	*Et*	80

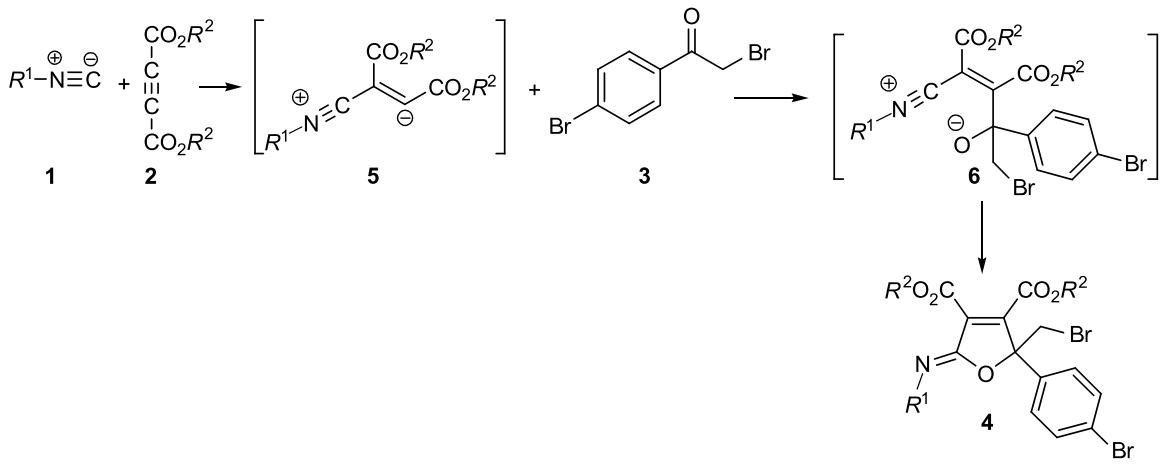
Scheme 1

heterocycles from common intermediates using isocyanide-based reactions [13] and electron deficient acetylenic esters [14] we report the synthesis of iminolactones **4** *via* the three-component condensation of isocyanides **1**, dialkyl acetylenedicarboxylates **2**, and 2-bromo-1-(4-bromophenyl)ethanone (**3**) in CH_2Cl_2 at room temperature in good isolated yields (Scheme 1).

Results and discussion

The structures of the products were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. The ^{1}H NMR spectrum of **4a** consisted of a multiplet signals for a cyclohexyl ring ($\delta = 1.21$–1.90 ppm), a multiplet for N–CH of cyclohexyl ring ($\delta = 3.65$–3.75 ppm), two methoxy groups ($\delta = 3.79$ and 3.92 ppm), two doublets for CH_2Br ($\delta = 4.08$ ppm, $^3J_{HH} = 11.0$ Hz and $\delta = 4.48$ ppm, $^3J_{HH} = 11.0$ Hz), and two doublets for phenyl ring ($\delta = 7.33$ ppm, $^3J_{HH} = 8.6$ Hz and $\delta = 7.52$ ppm, $^3J_{HH} = 8.6$ Hz). The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 19 distinct resonances, partial assignment of these resonances is given in the Experimental section.

Although the mechanism of the reaction between the isocyanide and dialkyl acetylenedicarboxylate in the presence of carbonyl groups has not yet been established experimentally, a possible pathway is proposed in Scheme 2. On the basis of the well established chemistry of isocyanides [15–18], it is



Scheme 2

reasonable to assume that initial formation of a highly reactive 1:1 zwitterionic intermediate **5** by the *Michael*-type addition reaction of the isocyanide **1** with the dialkyl acetylenedicarboxylate **2** which adds to the carbonyl group of 2-bromo-1-(4-bromophenyl)ethanone (**3**) leading to a dipolar species **6**. Cyclization of the latter leads to the iminolactones **4**.

In conclusion, we developed a new and general method for the preparation of the fully substituted iminolactones from the readily available dialkyl acetylenedicarboxylate, 2-bromo-1-(4-bromophenyl)-ethanone and isocyanides under neutral conditions without using any catalyst and activation. The reaction was shown to display good functional group tolerance, in high yielding, and product isolation is very straightforward.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in $CDCl_3$. Dialkyl acetylenedicarboxylate, isocyanides, and 2-bromo-1-(4-bromophenyl)ethanone (**3**) were purchased from Fluka and Merck and used without purification. All the products are new compounds, which were characterized by IR, ^{1}H, and ^{13}C NMR spectral data.

General prodedure

To a magnetically stirred solution of 0.28 g 2-bromo-1-(4-bromophenyl)ethanone (**3**, 1 mmol) and 1 mmol dialkyl acetylenedicarboxylate in 10 cm^3 CH_2Cl_2 was added, dropwise, a solution of 1 mmol isocyanide in 2 cm^3 CH_2Cl_2 at -10°C over 10 min. The mixture was allowed to warm up to room temperature and was finally stirred for 12 h. The solvent was removed under vacuum and the residue was crystallized from an *n*-hexane/ether (1/2) mixture and washed with ether (3×5 cm^3) and the products were thus obtained.

(5Z)-Dimethyl 2-(bromomethyl)-2-(4-bromophenyl)-5-(cyclohexylimino)-2,5-dihydrofuran-3,4-dicarboxylate

(**4a**, $C_{21}H_{23}Br_2NO_5$)

Colorless crystals, yield 0.51 g (97%); mp 132–134°C; IR (KBr): $\bar{\nu} = 2924$, 2849, 1750, 1720, 1680, 1440, 1294 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.21$–1.90 (m, $5CH_2$ of cyclohexyl), 3.65–3.75 (m, CH–N), 3.79, 3.92 (2s, $2OCH_3$), 4.08 (d, $^3J_{HH} = 11.0$ Hz, CH_2Br), 4.48 (d, $^3J_{HH} = 11.0$ Hz, CH_2Br), 7.33 (d, $^3J_{HH} = 8.6$ Hz, H–*Ar*), 7.52 (d, $^3J_{HH} = 8.6$ Hz, H–*Ar*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.77$, 24.80, 25.71, 32.88, 33.47 ($5CH_2$ of cyclohexyl), 38.26 (CH_2Br), 53.06, 53.16 ($2OCH_3$), 56.96 (CH–N), 89.54 (*C*–CH_2Br), 123.53, 127.57, 132.06, 135.80, 137.65, 142.47, 154.00 (C–*Ar*, C=C, C=N), 160.93, 161.94 (2C=O) ppm.

(5Z)-Diethyl 2-(bromomethyl)-2-(4-bromophenyl)-5-(cyclohexylimino)-2,5-dihydrofuran-3,4-dicarboxylate

(**4b**, $C_{23}H_{27}Br_2NO_5$)

Colorless crystals, yield 0.46 g (83%); mp 113–115°C; IR (KBr): $\bar{\nu} = 2929$, 2855, 1745, 1715, 1684, 1280 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$–1.90 (m, $5CH_2$ of cyclohexyl), 1.27 (t, $^3J_{HH} = 7.1$ Hz, OCH_2CH_3), 1.37 (t, $^3J_{HH} = 7.1$ Hz, OCH_2CH_3), 3.70–3.76 (m, CH–N), 4.09 (d, $^3J_{HH} = 11.0$ Hz, CH_2Br), 4.18–4.43 (m, $2OCH_2$-CH_3), 4.46 (d, $^3J_{HH} = 11.0$ Hz, CH_2Br), 7.35 (d, $^3J_{HH} = 8.6$ Hz, H–*Ar*), 7.53 (d, $^3J_{HH} = 8.6$ Hz, H–*Ar*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.80$, 14.07 ($2OCH_2CH_3$), 24.72, 24.75, 25.74, 32.90, 33.47 ($5CH_2$ of cyclohexyl), 36.39 (CH_2Br), 56.78 (CH–N), 62.23, 62.30 ($2OCH_2CH_3$), 89.50 (*C*–CH_2Br), 123.41, 127.65, 131.97, 136.00, 137.65, 142.20, 154.03 (C–*Ar*, C=C, C=N), 160.60, 161.56 (2C=O) ppm.

(5Z)-Dimethyl 5-(tert-butylimino)-2-(bromomethyl)-2-(4-bromophenyl)-2,5-dihydrofuran-3,4-dicarboxylate

(**4c**, $C_{19}H_{21}Br_2NO_5$)

Colorless crystals, yield 0.45 g (90%); mp 112–115°C; IR (KBr): $\bar{\nu} = 2967$, 1751, 1725, 1680, 1351, 1213 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.38$ (s, $C(CH_3)_3$), 3.78, 3.91 (2s, $2OCH_3$), 4.10 (d, $^3J_{HH} = 11.0$ Hz, CH_2Br), 4.46 (d, $^3J_{HH} = 11.0$ Hz, CH_2Br), 7.33 (d, $^3J_{HH} = 8.2$ Hz, H–*Ar*), 7.52 (d, $^3J_{HH} = 8.2$ Hz, H–*Ar*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.56$ ($C(CH_3)_3$), 36.32 (CH_2Br), 53.01, 53.06 ($2OCH_3$), 55.12 ($C(CH_3)_3$), 90.27 (*C*–CH_2Br), 123.40, 127.65, 131.98, 135.94, 138.98, 141.34, 151.82 (C–*Ar*, C=C, C=N), 160.93, 162.21 (2C=O) ppm.

(5Z)-Diethyl 5-(tert-butylimino)-2-(bromomethyl)-2-(4-bromophenyl)-2,5-dihydrofuran-3,4-dicarboxylate

(**4d**, $C_{21}H_{25}Br_2NO_5$)

Colorless crystals, yield 0.42 g (80%); mp 95–97°C; IR (KBr): $\bar{\nu} = 2971$, 1740, 1721, 1682, 1395, 1286 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (t, $^3J_{HH} = 7.1$ Hz, OCH_2CH_3), 1.36 (t, $^3J_{HH} = 7.1$ Hz, OCH_2CH_3), 1.38 (s, $C(CH_3)_3$), 4.12 (d, $^3J_{HH} = 11.1$ Hz, CH_2Br), 4.16–4.41 (m, $2OCH_2$-CH_3), 4.44 (d, $^3J_{HH} = 11.1$ Hz, CH_2Br), 7.35 (d, $^3J_{HH} = 8.6$ Hz, H–*Ar*), 7.52 (d, $^3J_{HH} = 8.6$ Hz, H–*Ar*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.78$, 14.10 ($2OCH_2CH_3$), 29.58 ($C(CH_3)_3$), 36.37 (CH_2Br), 55.06 ($C(CH_3)_3$), 62.18, 62.31 ($2OCH_2CH_3$), 90.30 (*C*–CH_2Br), 123.30, 127.73, 131.90, 136.09, 139.00, 141.30, 151.80 (C–*Ar*, C=C, C=N), 160.58, 161.77 (2C=O) ppm.

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