

Novel three-component synthesis of functionalized butynoates

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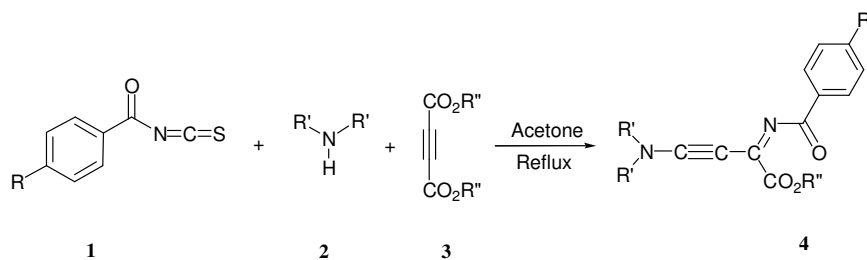
Abstract: An efficient synthesis of functionalized butynoates is described. This involves the three-component reaction of benzoyl isothiocyanates and secondary amines in the presence of activated acetylenes.

Keywords: Three-component reaction; Butynoates; Activated acetylenes; Secondary amines.

Introduction

N,N-Disubstituted-1-alkynylamines, the common name “Butynoates”, are regarded as the alkynes activated through the interaction of the amino group linked directly to a triple bond, and thereby liable to undergoing the reaction with a variety of electrophiles [1-5]. During recent decades, the preparation and synthetic utility of butynoates in organic and related fields have been explored [6]. However, synthetic application of butynoates remained relatively limited because of the difficulty experienced in their preparation and handling, due to their high reactivity and sensitivity toward hydrolysis [6d]. Thus, modification to thermally stable butynoates without decreasing the reactivity afforded a challenging

approach to improve their synthetic utility. An important example of this approach includes functionalized acetylenes containing “push-pull” systems, with an electron-donating group at one end and an electron-withdrawing group at the other end of the triple bond, as pioneered in Hsung [6c] and Ishihara [7]. As part of our current studies on the development of new routes in organic synthesis [8], we report an efficient synthesis of functionalized butynoates. Thus, the reaction of benzoyl isothiocyanate **1** and secondary amines **2** in the presence of dialkyl acetylenedicarboxylates **3** led to alkyl 2-[(benzoyl)imino]-4-dialkylamino-3-butynoate **4** in 55-72% yields (Scheme 1).



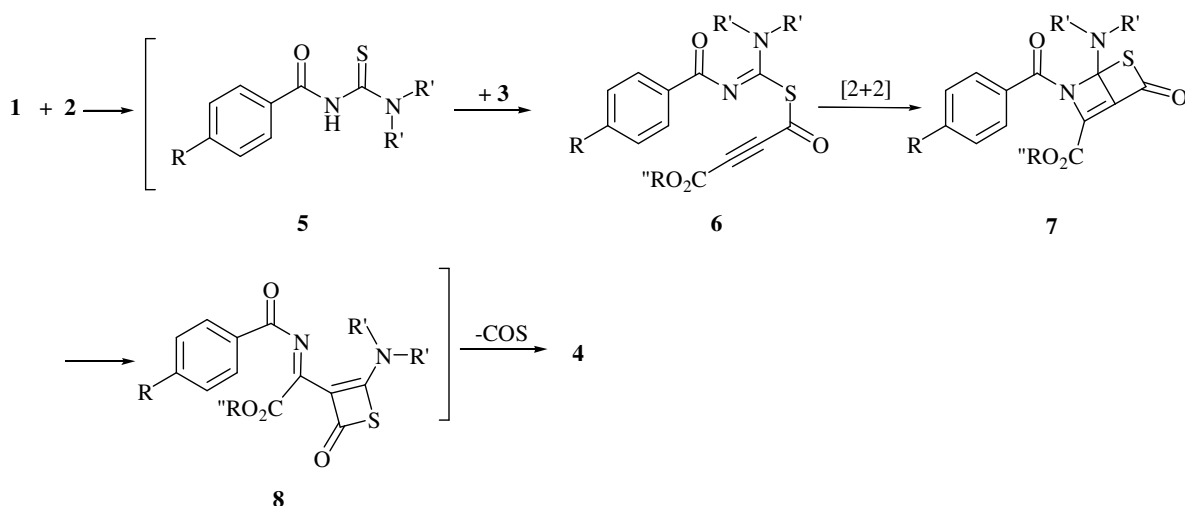
1, 2, 3, 4,	R	R'	R''	Yield (%) of 4
a	H	(CH ₂) ₅	Me	65
b	H	(CH ₂) ₅	Et	55
c	Me	(CH ₂) ₅	Me	67
d	NO ₂	(CH ₂) ₅	Me	56

Scheme 1.

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Structures of compounds **4a-4d** were assigned by IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and mass spectral data. For example, the $^1\text{H-NMR}$ spectrum of **4a** exhibited two broad multiplets ($\delta = 1.73$ and 3.61) for pentamethylene, a singlet ($\delta = 3.76$) for methoxy, and characteristic multiplets ($\delta = 7.39-7.76$) for the aromatic protons. The ^{13}C NMR spectrum of **4a** shows carbonyl ($\delta = 162.4$ and 170.8), imine ($\delta = 160.2$), and acetylenic ($\delta = 59.5$ and 109.1) carbons, in agreement with the butynoate structure.

Mechanistically, the reaction starts with addition of amine **2** to benzoyl isothiocyanate **1**, and generates the benzoylthiourea derivative **5** [9]. Subsequent nucleophilic attack of **5** to acetylenic compound **3** yields the 1:1 adducts **6**, which undergoes an intramolecular [2+2] cycloaddition [10] to produce the strained intermediate **7**. Electrocyclic ring opening [11] of **7** leads to **8**, which is finally converted to **4** by elimination of COS [13] (Scheme 2).



Scheme 2.

In conclusion, we have described a convenient route to functionalized butynoates from the three-component reaction of benzoyl isothiocyanates and secondary amines in the presence of dialkyl acetylenedicarboxylates. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The simplicity of the present procedure makes it an interesting alternative to other approaches. The procedure described here provides an acceptable method for the preparation of functionalized butynoates.

Experimental

Mp: Electrothermal-9100 apparatus; uncorrected. IR Spectra: Shimadzu IR-460 spectrometer. $^1\text{H-}$ and $^{13}\text{C-}$ NMR spectra: Bruker DRX-500 AVANCE instrument; in CDCl_3 at 500.1 and 125.7 MHz, resp.; δ 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. All chemicals were used as-received from the appropriate suppliers.

General procedure:

To a stirred solution of benzoyl isothiocyanate (2 mmol) and piperidine (2 mmol) in acetone (15 mL) dimethyl acetylenedicarboxylate (2 mmol) was added slowly and the reaction mixture was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2 ; hexane/AcOEt) to afford **4a**. Yield: 0.39 g (65%); colorless crystals, mp $101-103^\circ\text{C}$, IR (KBr): $1702, 1521, 1244\text{ cm}^{-1}$. $^1\text{H-NMR}$: $\delta = 1.73$ (broad s, 3 CH_2), 3.61 (broad s, 2 CH_2), 3.76 (s, OCH_3), $7.39-7.45$ (m, 3 CH), 7.76 (dd, $^3J = 9.5$, $^4J = 2.4$, 2 CH), $^{13}\text{C-NMR}$: $\delta = 23.9$ (CH_2), 25.1 (2 CH_2), 49.2 (2 CH_2), 51.5

(OMe), 59.5 (C), 109.1 (C), 127.5 (2 CH), 128.9 (CH), 129.8 (2 CH), 134.8 (C), 160.2 (C=N), 162.4, 170.8 (2 C=O). EI-MS: 298(M⁺, 4); 137 (85); 105(30); 97 (40); 69 (45), 57 (100). Anal. Calcd for C₁₇H₁₈N₂O₃ (298.34): C, 68.44; H, 6.08; N, 9.39; found: C, 68.50; H, 6.10; N, 9.42%. Similarly, the following compounds were prepared. All compounds gave satisfactory analytical and spectroscopic data.

Compound **4b**: Yield: 0.34 g (55%); yellow powder, mp 98-100°C, IR (KBr): 1702, 1521, 1244 cm⁻¹. ¹H-NMR: δ = 1.25 (t, ³J = 8.8, 3 CH), 1.69 (broad, 3 CH₂), 3.59 (broad, 2 CH₂), 4.24 (q, ³J = 8.8, 2 CH), 7.36-7.42 (m, 3 CH), 7.74 (dd, ³J = 9.4, ⁴J = 2.1, 2 CH). ¹³C-NMR: δ = 14.2 (Me), 22.9 (CH₂), 25.1 (2 CH₂), 49.2 (2 CH₂), 63.2 (OCH₂), 68.1, 109.7 (2 C), 127.4 (2 CH), 128.8 (CH), 129.8 (2 CH), 134.8 (C), 161.9 (C=N), 167.7, 170.7 (2 C=O).

Compound **4c**: Yield: 0.42 g (67%); yellow powder; mp 85-86°C. IR (KBr): 1703, 1695, 1539, 1239 cm⁻¹. ¹H-NMR: δ = 1.67 (broad, 3 CH₂), 2.37 (s, CH₃), 3.55 (broad, 2 CH₂), 3.72 (s, OCH₃), 7.19 (d, ³J = 7.9, 2 CH), 7.64 (d, ³J = 7.9, 2 CH). ¹³C-NMR: δ = 21.4 (CH₃), 24.0 (CH₂), 25.1 (2 CH₂), 49.2 (2 CH₂), 51.5 (OMe), 60.1, 108.7 (2 C), 128.3 (2 CH), 129.7 (2 CH), 132.1, 133.6 (2 C), 160.6 (C=N), 162.5, 170.9 (2 C=O).

Compound **4d**: Yield: 0.38 g (56%); Yellow powder; mp 115-117°C. IR (KBr): 1690, 1607, 1550, 1240 cm⁻¹. ¹H-NMR: δ = 1.69 (broad s, 3 CH₂), 3.57 (broad s, 2 CH₂), 3.73 (s, OCH₃), 7.92 (d, ³J = 8.7, 2 CH), 8.22 (d, ³J = 8.7, 2 CH). ¹³C-NMR: δ = 23.9 (CH₂), 25.1 (2 CH₂), 49.3 (2 CH₂), 51.8 (OMe), 59.6, 110.8 (2 C), 122.7 (2 CH), 130.9 (2 CH), 141.2, 147.8 (2 C), 157.4 (C=N), 162, 171.1 (2 C=O). EI-MS: 343 (M⁺, 5); 152 (30); 137 (80); 97 (35); 71 (34), 69 (50), 57 (100). Anal. Calcd for C₁₇H₁₇N₃O₅ (343.34): C, 59.47; H, 4.99; N, 12.24; found: C, 59.37; H, 4.91; N, 12.30%.

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