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Efficient synthesis of 2,3,4-trisubstituted furans from the reaction of activated acetylenes with ethyl bromopyruvate in the presence of enaminones

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Abstract The reaction of dialkyl acetylenedicarboxylates or diaroylacetylenes with ethyl bromopyruvate in the presence of enaminones led to 2-ethyl 3,4-dialkyl 4-bromo-4,5-dihydro-2,3,4-furantricarboxylates or ethyl 3,4-diaroyl-4-bromo-4,5-dihydro-2-furancarboxylate in excellent yields. These compounds are quantitatively converted to the corresponding 2,3,4-trisubstituted furans by 4-dimethylaminopyridine.

Keywords Ethyl bromopyruvate; Activated acetylenes; Trisubstituted furans; Enaminone.

Introduction

Highly substituted furans play an important role in organic chemistry, not only as key structural units in many natural products, common subunits in pharmaceuticals [1–7], fragrances [8], and flavors [9], but also as useful building blocks in synthetic chemistry [10–14]. They have also found utility as synthetic intermediates or synthons for numerous functional groups, *inter alia*, carboxylic acids, α-keto-esters, and aromatics [15]. For this reason, the efficient synthesis of multiply substituted furans continues to attract the interest of synthesis chemists [16, 17].

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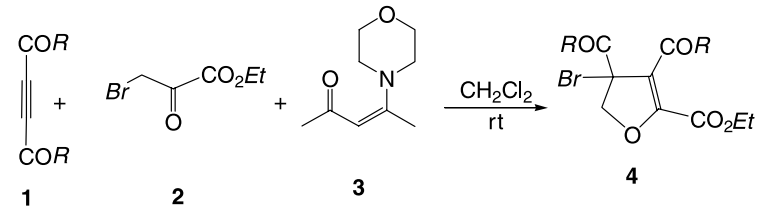
Results and discussion

As part of our current studies on the development of new routes in heterocyclic synthesis [18–21], we report an efficient synthesis of 2,3,4-trisubstituted furans. Thus, the reaction of dialkyl acetylenedicarboxylates **1a**–**1c** or diaroylacetylenes **1d**–**1e** [22, 23], with ethyl bromopyruvate [2] in the presence of enaminones 3 [24] led to 2-ethyl 3,4-dialkyl 4-bromo-4,5-dihydro-2,3,4-fur-tricarboxylates **4a**–**4c** or ethyl 3,4-diaroyl-4-bromo-4,5-dihydro-2-furoates **4d**–**4e**, in excellent yields. These compounds are quantitatively converted to the corresponding 2,3,4-trisubstituted furans 5 by 4-dimethylaminopyridine (Scheme 1).

The structures of compounds **4a**–**4e** and **5a**–**5e** were apparent from their mass spectra, which displayed in each case, the molecular ion peak at the appropriate m/z values. The ^{1}H and ^{13}C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. The ^{1}H NMR spectrum of **4a** exhibited two singlets ($\delta = 3.59$ and 3.80 ppm) arising from the methoxy proton, along with two doublets ($\delta = 4.44$ ppm) and 4.64 ($^2J_{HH} = 10.8$ Hz) for the diastereotopic methylene protons. The carbonyl groups resonances in the ^{13}C NMR spectra of **4a** appear at $\delta = 160.0$, 162.1, and 171.5 ppm. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 337$, which is consistent with the 1:1 adduct of ethyl bromopyruvate and **1a**.

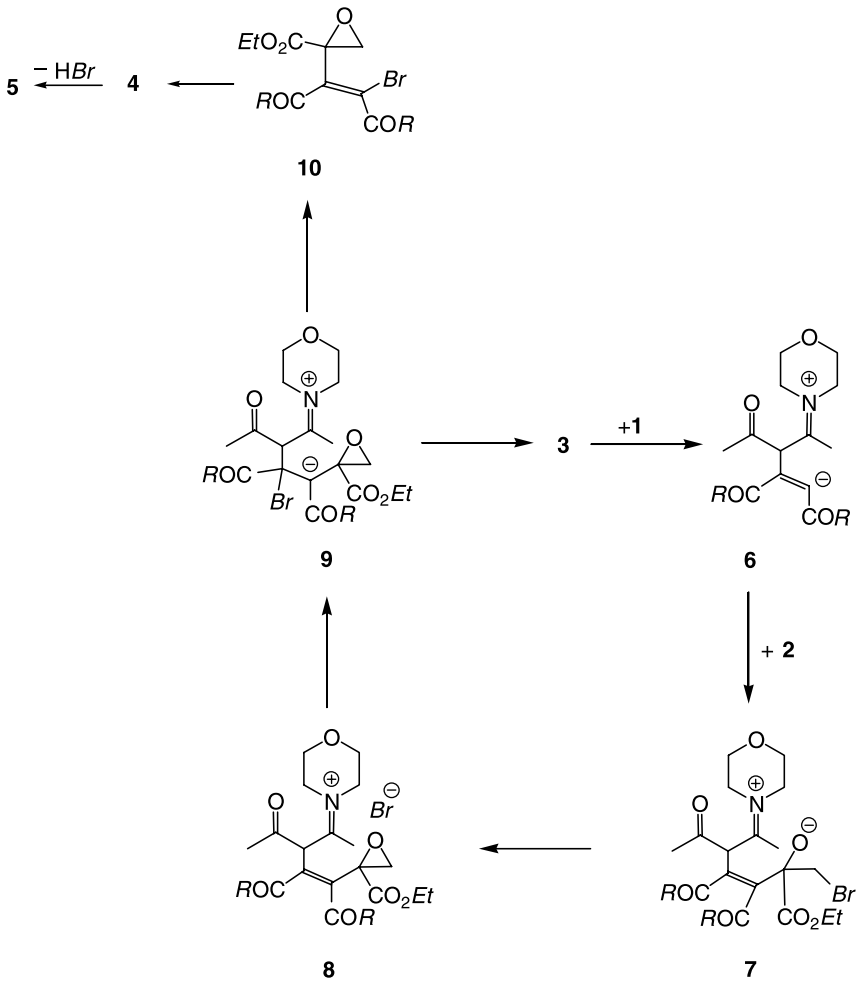
The ^{1}H NMR spectrum of **5a** exhibited three singlets for methoxy ($\delta = 3.60$ and 3.75 ppm) and



1, 4, 5	R	Yield/% of 4	Yield/% of 5
a	O*Me*	84	81
b	O*Et*	78	75
c	O^t*Bu*	82	78
d	*Ph*	85	74
e	*p*-Tolyl	92	80

Scheme 1

methine ($\delta = 7.53$ ppm) protons, along with characteristic signals of the ethoxy group. The ^{13}C signals of carbonyl groups in **5a** appear at $\delta =$ 161.9, 168.6, and 168.7 ppm. The mass spectrum of **4a** displayed the molecular ion peak at $m/z = 256$.



Scheme 2

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1,3-dipolar intermediate [25] **6** between the enaminone and the electron-deficient acetylenic compound, which reacts with the carbonyl group of **2** to generate **7**. This intermediate undergoes a *Darzens*-type reaction to produce **8**, which losses the enaminone moiety *via* **9** to generate **10**. Electrocyclization of **10** leads to **4**, which is converted to **5** by loss of HBr in the presence of 4-dimethylaminopyridine (Scheme 2).

In conclusion, the reaction of dialkyl acetylenedicarboxylates or diaroylacetylenes with **2** in the presence of enaminones led to 4-bromo-4,5-dihydro-furan derivatives, in excellent yields. In the presence of 4-dimethylaminopyridine, these compounds are quantitatively converted to 2,3,4-trisubstituted furans. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

Experimental

Dibenzoylacetylene was prepared according to Refs. [22, 23]. Other chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 aparatus. Elemental analyses for the C and H were performed using a *Heraeus* CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. Mass spectra were recorded on a Finnigan-Mat 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, and ^{13}C NMR spectra were measured with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz.

*General procedure for the preparation of **4***

To a stirred solution of 2 mmol dialkyl acetylenedicarboxylate or diaroyl acetylene and 0.390 g ethyl bromopyruvate (2 mmol) in 15 cm^3 of CH_2Cl_2 was added the 2 mmol enaminone at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; *n*-hexane:*Ac*O*Et*, 9:1) to afford 4.

2-Ethyl 3,4-dimethyl 4-bromo-4,5-dihydro-2,3,4-furantricarboxylate (**4a**, $C_{11}H_{13}BrO_7$)

Yellow oil, yield 0.55 g, 81%; IR (KBr): $\bar{\nu} = 1735$, 1733, 1729, 1636, 1582 cm^{-1}; EI-MS: m/z (%) = 339 (M+2, 5), 337 (M^+, 5), 306 (66), 292 (64), 275 (85), 257 (62), 45 (84), 31 (100); ^{1}H NMR: $\delta = 1.17$ (t, $^3J = 7.2$, *Me*), 3.59 (s, O*Me*), 3.80 (s, O*Me*), 4.21 (q, $^3J = 7.2$, CH_2O), 4.44 (d, $^2J = 10.8$, CH), 4.64 (d, $^2J_{HH} = 10.8$, CH) ppm; ^{13}C NMR: $\delta = 13.8$ (*Me*), 51.6 (O*Me*), 52.9 (O*Me*), 63.1 (OCH_2), 81.9 (CH_2), 82.2 (C), 111.9 (C), 158.3 (C), 160.0 (C=O), 162.1 (C=O), 171.5 (C=O) ppm.

2-Ethyl 3,4-diethyl 4-bromo-4,5-dihydro-2,3,4-furantricarboxylate (**4b**, $C_{13}H_{17}BrO_7$)

Yellow oil, yield 0.54 g, 75%; IR (KBr): $\bar{\nu} = 1734$, 1730, 1725, 1634, 1575 cm^{-1}; EI-MS: m/z (%) = 367 (M+2, 15), 365 (M^+, 15), 320 (5), 285 (76), 230 (64), 135 (58), 45 (100); ^{1}H NMR: $\delta = 0.98$ (t, $^3J = 7.5$, *Me*), 1.04 (t, $^3J = 7.3$, *Me*), 1.12 (t, $^3J_{HH} = 7.2$, *Me*), 3.99 (q, $^3J = 7.2$, OCH_2), 4.03 (q, $^3J = 7.5$, OCH_2), 4.14 (q, $^3J = 7.3$, OCH_2), 4.32 (d, $^2J = 10.8$, CH), 4.51 (d, $^2J = 10.8$, CH) ppm; ^{13}C NMR: $\delta = 13.5$ (*Me*), 13.7 (*Me*), 13.8 (*Me*), 60.1 (OCH_2), 61.9 (OCH_2), 62.3 (OCH_2), 82.0 (CH_2), 82.1 (C), 113.0 (C), 158.4 (C), 161.6 (C=O), 162.1 (C=O), 171.4 (C=O) ppm.

2-Ethyl 3,4-di(tert-butyl)4-bromo-4,5-dihydro-2,3,4-furantricarboxylate (**4c**, $C_{17}H_{25}BrO_7$)

Yellow oil, yield 0.66 g, 78%; IR (KBr): $\bar{\nu} = 1730$, 1725, 1720, 1636, 1579 cm^{-1}; EI-MS: m/z (%) = 423 (M+2, 15), 421 (M^+, 15), 376 (76), 341 (46), 364 (82), 348 (65), 275 (64), 73 (34), 57 (100), 45 (84); ^{1}H NMR: $\delta = 1.39$ (3*Me*), 1.46 (t, $^3J = 7.2$, *Me*), 1.51 (3*Me*), 4.16–4.29 (m, OCH_2), 4.43 (d, $^2J = 10.7$, CH), 4.62 (d, $^2J = 10.7$, CH) ppm; ^{13}C NMR: $\delta = 13.9$ (*Me*), 27.8 (3*Me*), 28.0 (3*Me*), 62.8 (OCH_2), 81.1 (CH_2), 81.6 (C), 82.6 (CMe_3), 84.1 (CMe_3), 112.2 (C), 158.6 (C), 161.1 (C=O), 164.2 (C=O), 172.1 (C=O) ppm.

2-Ethyl 3,4-dibenzoyl-4-bromo-4,5-dihydro-2,3,4-furantricarboxylate (**4d**, $C_{21}H_{17}BrO_5$)

Yellow powder, yield 0.64 g, 74%; IR (KBr): $\bar{\nu} = 1726$, 1660, 1635, 1563, 1506, 1434 cm^{-1}. EI-MS: m/z (%) = 431 (M+2, 5), 429 (M^+, 5), 384 (82), 352 (46), 349 (58), 324 (66), 219 (35), 45 (64), 105 (100); ^{1}H NMR: $\delta = 1.16$ (t, $^3J_{HH} = 7.3$, *Me*), 4.21 (q, $^3J = 7.3$, OCH_2), 4.41 (d, $^2J = 10.5$, CH), 4.63 (d, $^2J = 10.5$, CH), 7.41 (t, $^3J = 7.2$, 2CH), 7.47–7.63 (m, 4 CH), 7.88 (d, $^3J = 7.3$, 2CH). 8.07 (d, $^3J = 7.3$, 2CH) ppm; ^{13}C NMR: $\delta = 13.8$ (*Me*), 63.0 (OCH_2), 81.7 (CH_2), 82.0 (C), 120.9 (C), 128.2 (2CH), 128.5 (2CH), 128.7 (2CH), 129.5 (2CH), 132.1 (CH), 134.0 (CH), 136.1 (C), 139.2 (C), 154.6 (C), 168.7 (C=O), 187.6 (C=O), 194.4 (C=O) ppm.

2-Ethyl 3,4-di(4-methylbenzoyl)-4-bromo-4,5-dihydro-2,3,4-furantricarboxylate (**4e**, $C_{23}H_{21}BrO_5$)

Orange powder, yield 0.73 g, 80%; IR (KBr): $\bar{\nu} = 1732$, 1697, 1638, 1575, 1432 cm^{-1}; EI-MS: m/z (%) = 459 (M+2, 10), 457 (M^+, 10), 412 (66), 377 (56), 337 (85), 217 (64), 120 (34), 45 (100); ^{1}H NMR: $\delta = 1.32$ (t, $^3J = 7.2$, *Me*), 2.38 (*Me*), 2.43 (*Me*), 4.28 (q, $^3J = 7.2$, OCH_2), 4.39 (d, $^2J = 10.6$, CH), 4.63 (d, $^2J = 10.6$, CH), 7.19 (d, $^3J = 7.2$, 2CH), 7.29 (d, $^3J = 7.2$, 2CH), 7.77 (d, $^3J = 7.2$, 2CH), 7.93 (d, $^3J = 7.2$, 2CH) ppm; ^{13}C NMR: $\delta = 14.1$ (*Me*), 21.4 (*Me*), 22.1 (*Me*), 63.4 (OCH_2), 82.5 (CH_2), 83.1 (C), 121.1 (C), 127.1 (2CH), 128.5 (2CH), 130.6 (2CH), 130.9 (2CH), 133.6 (C), 138.5 (C), 1143.0 (C), 143.4 (C), 154.2 (C), 161.7 (C=O), 189.1 (C=O), 193.2 (C=O) ppm.

*General procedure for the preparation of **5***

To a stirred solution of 2 mmol **4** in 15 cm^3 CH_2Cl_2 was added the 2 mmol 4-dimethylaminopyridine at room temperature. The reaction mixture was then stirred for 12 h. The solvent

was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; *n*-hexane:*Ac*O*Et*, 10:1) to afford **5**.

2-Ethyl 3,4-dimethyl 2,3,4-furantricarboxylate (**5a**, $C_{11}H_{12}O_7$) Yellow oil, yield 0.43 g, 84%; IR (KBr): $\bar{\nu} = 1732$, 1730, 1727 cm^{-1}; EI-MS: m/z (%) = 256 (M^+, 10), 225 (64), 211 (82), 194 (64), 45 (86), 31 (100); ^{1}H NMR: $\delta = 1.16$ (t, $^3J = 7.2$, *Me*), 3.60 (O*Me*), 3.75 (O*Me*), 4.19 (q, $^3J = 7.2$, OCH_2), 7.53 (*s*, CH) ppm; ^{13}C NMR: $\delta = 13.7$ (*Me*), 51.5 (O*Me*), 53.0 (O*Me*), 62.9 (OCH_2), 112.5 (C), 117.9 (C), 154.6 (C), 158.5 (CH), 161.9 (C=O), 168.6 (C=O), 168.7 (C=O) ppm.

2-Ethyl 3,4-diethyl 2,3,4-furantricarboxylate (**5b**, $C_{13}H_{16}O_7$) Yellow oil, yield 0.44 g, 78%; IR (KBr): $\bar{\nu} = 1730$, 1725, 1720 cm^{-1}; EI-MS: m/z (%) = 284 (M^+, 15), 239 (76), 194 (85), 149 (54), 135 (62), 90 (62), 45 (100); ^{1}H NMR: $\delta = 0.97$ (t, $^3J = 7.5$, *Me*), 1.09 (t, $^3J = 7.3$, *Me*), 1.14 (t, $^3J = 7.2$, *Me*), 3.82 (q, $^3J = 7.2$, OCH_2), 3.90 (q, $^3J = 7.5$, OCH_2), 4.12 (q, $^3J = 7.3$, OCH_2), 7.32 (*s*, CH) ppm; ^{13}C NMR: $\delta = 13.4$ (*Me*), 13.6 (*Me*), 13.8 (*Me*), 61.1 (OCH_2), 61.7 (OCH_2), 62.3 (OCH_2), 111.5 (C), 113.1 (C), 153.2 (C), 159.1 (CH), 161.6 (C=O), 168.1 (C=O), 169.4 (C=O) ppm.

2-Ethyl 3,4-di(tert-butyl)- 2,3,4-furantricarboxylate (**5c**, $C_{17}H_{24}O_7$) Yellow oil, yield 0.56 g, 82%; IR (KBr): $\bar{\nu} = 1725$, 1720, 1715 cm^{-1}; EI-MS: m/z (%) = 340 (M^+, 5), 295 (34), 283 (86), 267 (64), 194 (54), 146 (46), 73 (98), 45 (64), 57 (100); ^{1}H NMR: $\delta = 1.15$ (t, $^3J = 7.2$, *Me*), 1.32 (3*Me*), 1.48 (3 *Me*), 4.26 (q, $^3J = 7.2$, OCH_2), 7.42 (*s*, CH) ppm; ^{13}C NMR: $\delta = 14.2$ (*Me*), 27.5 (3*Me*), 27.8 (3*Me*), 62.5 (OCH_2), 82.3 (CMe_3), 83.1 (CMe_3), 111.2 (C), 113.6 (C), 154.2 (C), 157.9 (CH), 162.0 (C=O), 163.9 (C=O) 166.3 (C=O) ppm.

Ethyl 3,4-dibenzoyl-2-furoate (**5d**, $C_{21}H_{16}O_5$) Yellow oil, yield 0.59 g, 85%; IR (KBr): $\bar{\nu} = 1725$, 1668, 1654 cm^{-1}; EI-MS: m/z (%) = 348 (M^+, 5), 303 (56), 271 (85), 243 (86), 45 (46), 105 (100); ^{1}H NMR: $\delta = 1.16$ (t, $^3J = 7.3$, *Me*), 4.21 (q, $^3J = 7.3$, OCH_2), 6.20 (s, CH), 7.36 (t, $^3J = 7.2$, 2CH), 7.40–7.65 (*m*, 4CH), 7.85 (d, $^3J = 7.3$, 2CH), 8.12 (d, $^3J = 7.3$, 2CH) ppm; ^{13}C NMR: $\delta = 13.7$ (*Me*), 63.5 (OCH_2), 117.9 (C), 121.2 (C), 128.2 (2CH), 128.5 (2CH), 128.7 (2CH), 129.5 (2CH), 132.1 (CH), 134.0 (CH), 136.1 (C), 139.2 (C), 154.6 (C), 159.4 (CH), 169.7 (C=O), 188.6 (C=O), 191.2 (C=O) ppm.

Ethyl 3,4-di(4-methylbenzoyl)-2-furoate (**5e**, $C_{23}H_{20}O_5$) Yellow oil, yield 0.69 g, 92%; IR (KBr): $\bar{\nu} = 1727$, 1690, 1665 cm^{-1}; EI-MS: m/z (%) = 376 (M^+, 15), 331 (74), 256 (85), 136 (62), 120 (100); 45 (82); ^{1}H NMR: $\delta = 1.32$ (t, $^3J = 7.2$, *Me*), 2.38 (*Me*), 2.43 (*Me*), 4.28 (q, $^3J = 7.2$, OCH_2), 6.17 (*s*, CH), 7.19 (d, $^3J = 7.2$, 2CH), 7.29 (d, $^3J = 7.2$, 2CH), 7.77 (d, $^3J = 7.2$, 2CH), 7.93 (d, $^3J = 7.2$, 2CH) ppm; ^{13}C NMR: $\delta = 14.1$ (*Me*), 21.4 (*Me*), 22.1 (*Me*), 63.4 (OCH_2), 119.4 (C), 121.1 (C), 127.1 (2CH), 128.5 (2CH), 130.6 (2CH), 130.9 (2CH), 135.2 (C), 133.6 (C), 138.5 (C), 143.0 (C), 154.2 (C), 158.9 (CH), 162.5 (C=O), 190.1 (C=O), 192.8 (C=O) ppm.

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