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# Reaction of *tert*-butyl isocyanide and dialkyl acetylenedicarboxylates in the presence of 2-acetylbutyrolactone. Synthesis of functionalized α-methylene-γ-butyrolactones

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**Abstract**—Reaction of *tert*-butyl isocyanide with dialkyl acetylenedicarboxylates in the presence of 2-acetylbutyrolactone leads to the formation of dialkyl (*E*)-2-{(*tert*-butylamino)[2-oxo-4,5-dihydro-3(2*H*)-furanylidene]methyl}-2-butenedioates.


Multicomponent reactions (MCRs), by virtue of their convergence, productivity easy execution and generally high yields of products, have attracted much attention from the point of view of combinatorial chemistry. Of pivotal importance in this area are the isocyanide based MCRs such as the versatile *Ugi* and *Passerini* reactions.[1–4] The addition of nucleophilic carbenes such as isocyanides to dialkyl acetylenedicarboxylates has been investigated in detail by a number of research groups.[5–7]

The three-component reaction of tricarbonyl compounds with *tert*-butyl isocyanide and acetylenic diesters has been previously reported.[8] The products of the above reaction are ketenimines **1**. Now, we report the reaction of 2-acetylbutyrolactone with isonitrile and acetylene diesters. The products were not ketenimines such as **2** but α-methylene-γ-butyrolactones **5** (Scheme 1).[9]

The α-methylene-γ-butyrolactone moiety is known to be responsible for various biological activities such as antitumour,[10] phytotoxic[11] and antibacterial.[12] Moreover, they are useful as synthetic intermediates.[13]

The reaction of *tert*-butyl isocyanide with acetylenic diesters **3** in the presence of 2-acetylbutyrolactone **4** gave compounds **5a**–**c**. On the basis of the well established chemistry of isocyanides,[14,15] it is reasonable to assume that **5** results from initial addition of the *tert*-butyl isocyanide to the acetylenic diesters and subsequent protonation of the 1:1 adduct by the enolized keto-ester. Next, the positively charged cationic species produced could react at carbon with the enolate anion of **4**, producing **6**. Under the reaction conditions, compounds **6** could react with $H_2O$, losing the acetyl group as acetic acid, and compounds **5** would be produced (Scheme 2).

The structures of compounds **5** were deduced from mass spectrometric, $^1H$ and $^{13}C$ NMR and IR data. The $^1H$ NMR spectrum of **5a** exhibited a singlet at $\delta$ 1.25 ppm for the *tert*-butyl group, two singlets at $\delta$ 3.78 and 3.86 ppm for the two methoxy groups, two triplets at $\delta$ 2.53 and 4.22 ppm for $CH_2$ and $OCH_2$ groups butyrolactone moiety, a singlet $\delta$ 7.01 ppm for the olefinic proton and a broad resonance for NH group at $\delta$ 8.40 ppm. The $^{13}C$ NMR spectrum **5a** showed signals for *tert*-butyl (31.35 ppm), methoxy (52.42 and 53.31 ppm) and olefinic carbons (87.49, 131.87, 139.20 and 150.87) in agreement with the proposed structure. In the IR spectrum of **5a**, of special interest, were the absorption bands at 3250 $cm^{-1}$ and at 1720–1735 $cm^{-1}$ for C=O groups. The mass spectrum of **5a** confirmed its molecular weight, at $m/e = 311$. The $^1H$ NMR, $^{13}C$ NMR and IR spectra of **5b**–**c** were similar to that of **5a**, except for the ester moieties.

In conclusion, we have developed a simple and efficient method for the preparation of functionalized α-methylene-γ-butyrolactones. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and

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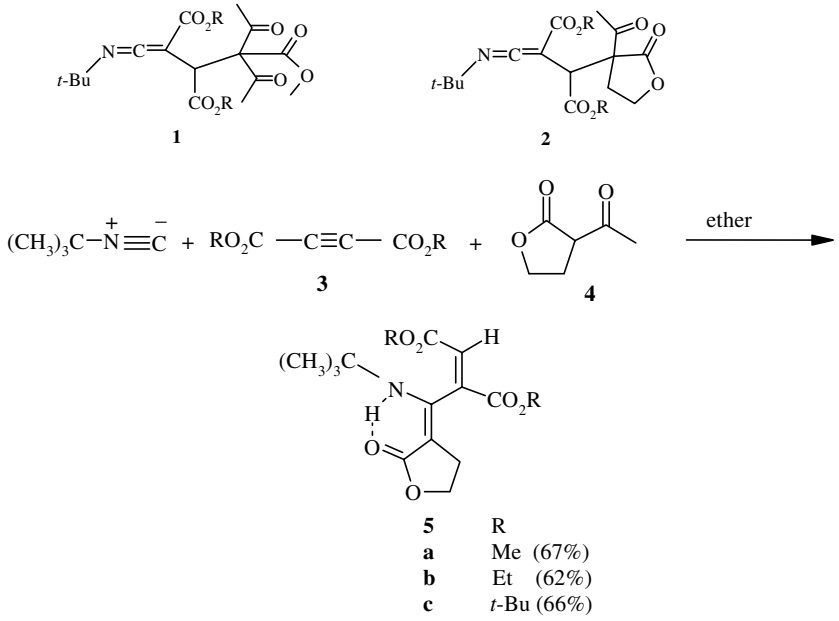
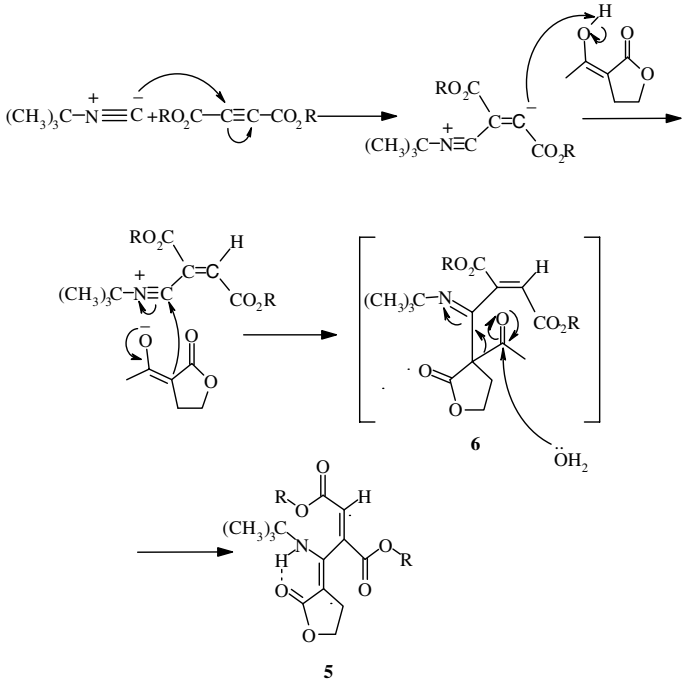



**Scheme 1.**




**Scheme 2.**

reagents can be mixed without any activation or modification.

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9. *Representative experimental procedure*: Preparation of (*E*)-2-{(*tert*-butylamino)[2-oxo-4,5-dihydro-3(2*H*)-furanylidene]methyl]}-2-butenedioates (exemplified by **5a**): To a magnetically stirred solution of dimethyl acetylenedicarb-

oxylate (2 mmol) and 2-acetylbutyrolactone (0.256 g, 2 mmol) in ether (5 ml) was added, dropwise, *tert*-butyl isocyanide (0.17 g, 2 mmol) at −10 °C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. Next, a little amount of water (some droplets) was added to the reaction mixture and stand for 24 h. The solvent was removed under reduced pressure and the resulting mixture of products obtained as a yellow viscous oil, was purified by silica gel (Merck silica gel, 230–400 mesh) column chromatography using hexane:ethyl acetate as eluent. The solvent was removed under reduced pressure to give **5a** as a yellow powder, yield 0.417 g (67%), mp: 94–96 °C; IR (KBr): ($\nu_{max}$/cm$^{-1}$) = 3250 (NH), 1735 (C=O), 1666 (C=C), $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H = 1.25$ (9H, s, $CMe_3$), 2.53 (2H, t, $^3J_{HH} = 7.8$ Hz, $CH_2$), 3.78 (3H, s, OMe), 3.86 (3H, s, OMe), 4.22 (2H, t, $^3J_{HH} = 7.8$ Hz, $OCH_2$), 7.01 (1H, s, CH), 8.40 (1H, br s, NH), $^{13}$C NMR (125.77 MHz): $\delta_C = 26.55$ ($CH_2$), 31.35 ($CMe_3$), 52.42 and 53.31 (2OMe), 53.24 ($NCMe_3$), 65.23 ($OCH_2$), 87.49, 131.87, 139.20 and 150.87 (olefinic carbons), 163.9 and 164.59 (C=O, esters), 173.7 (C=O, lactone), MS (EI, 70 eV): *m/z* (%) = 311 ($M^+$, 4), 296 (M−$CH_3$, 10), 254 (M−$C_4H_9$, 12), 196 [M−(OEt+$C_4H_9O_2$), 100], 57 ($C_4H_9^+$, 68). Anal. Calcd for $C_{15}H_{21}NO_6$ (311.33): C, 57.87, H, 6.80, N, 4.50. Found: C, 57.64, H, 6.78, N, 4.49. Compound **5b**: Yellow powder, yield 0.42 g (62%), mp: 79–81 °C; IR (KBr): ($\nu_{max}$/cm$^{-1}$) = 3220 (NH), 1726 (C=O), 1650 (C=C), $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H = 1.24$ (9H, s, $CMe_3$), 1.29 (3H, t, $^3J_{HH} = 7.2$ Hz, $CH_3$), 1.33 (3H, t, $^3J_{HH} = 7.2$ Hz, $CH_3$), 2.55 (2H, t, $^3J_{HH} = 7.9$ Hz, $CH_2$), 4.18–4.41 (6H, m, 3$OCH_2$), 6.99 (1H, s, CH), 8.37 (1H, br s, NH); $^{13}$C NMR (125.77 $CH_2$); $\delta_C = 13.97$ and 14.09 (2$CH_3$), 26.62 ($CH_2$), 31.12 ($CMe_3$), 53.25 ($NCMe_3$), 61.58, 62.51 and 65.23 (3$OCH_2$), 87.41, 132.08, 139.09 and 151.172 (olefinic carbons), 163.73 and 164.01 (2C=O, esters), 173.68 (C=O, lactone), MS (EI, 70 eV): *m/z* (%) = 339 ($M^+$, 20), 324 (M−$CH_2$, 23), 282 (M−$C_4H_9$, 77), 226 [M−(Et+$C_4H_4O_2$), 88], 210 [M−(OEt+$C_4H_4O_2$), 100], 191 [M−($C_4H_4O_2$+$C_4H_9$), 70], 57 ($C_4H_9^+$, 71), 29 ($C_2H_5^+$, 36). Anal. Calcd for $C_{17}H_{25}NO_6$ (339.39): C, 60.16, H, 7.42, N, 4.13. Found: C, 59.93, H, 7.40, N, 4.12. Compound **5c**: Yellow powder, yield 0.513 g (66%), mp: 99–101 °C; IR (KBr): ($\nu_{max}$, cm$^{-1}$) = 3290 (NH), 1720 (C=O), 1670 (C=C), $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H = 1.27$ (9H, s, $NHCMe_3$), 1.46 (9H, s, $OCMe_3$), 1.51 (9H, s, $OCMe_3$), 2.57 (2H, tt, $^3J_{HH} = 7.8$ and $^6J_{HH} = 3.2$ Hz, $CH_2$), 4.22 (2H, t, $^3J_{HH} = 7.8$ Hz, $OCH_2$), 6.80 (1H, s, CH), 8.37 (1H, br s, NH), $^{13}$C NMR (125.77 MHz): $\delta_C = 26.71$ ($CH_2$), 27.84 and 27.86 (2$OCMe_3$), 31.23 ($NCMe_3$), 53.19 ($NCMe_3$), 65.21 ($OCH_2$), 82.79 and 83.26 (2$OCMe_3$), 87.02, 132.96, 138.98 and 152.18 (olefinic carbons), 163.0 and 163.31 (2C=O, ester), 173.17 (C=O, lactone); MS (EI, 70 eV): *m/z* (%) = 395 ($M^+$, 19) 282 (M−2$C_4H_8$, 38), 268 [M−($C_4H_8$+$NCMe_3$), 66], 226 [M−(2$C_4H_8$+$C_4H_9$), 77], 182 [M−($OCMe_3$+$C_4H_8$+$C_4H_4O_2$), 100], 57 ($C_4H_9^+$, 88). Anal. Calcd for $C_{21}H_{33}NO_6$ (395.50): C, 63.78, H, 8.41, N, 3.54. Found C, 63.53, H, 8.38, N, 3.53.


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