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A New and Efficient One-pot Synthesis of Trialkyl 6-*tert*-Butylamino-2*H*-pyran-2-one-3,4,5-tricarboxylates†

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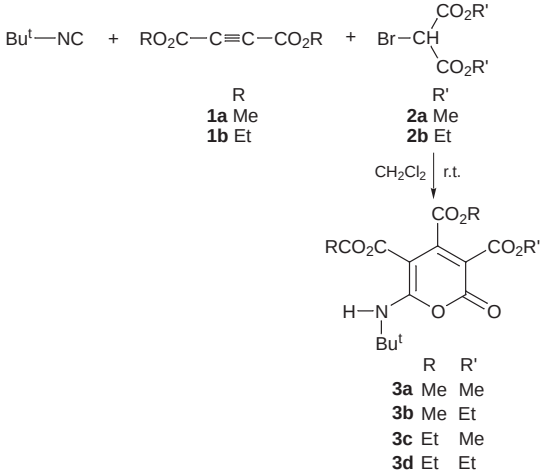
The highly reactive 1:1 intermediate produced in the reaction between *tert*-butyl isocyanide and dialkyl acetylenedicarboxylates is trapped by dialkyl 2-bromomalonates to yield the title compounds in fairly high yields.

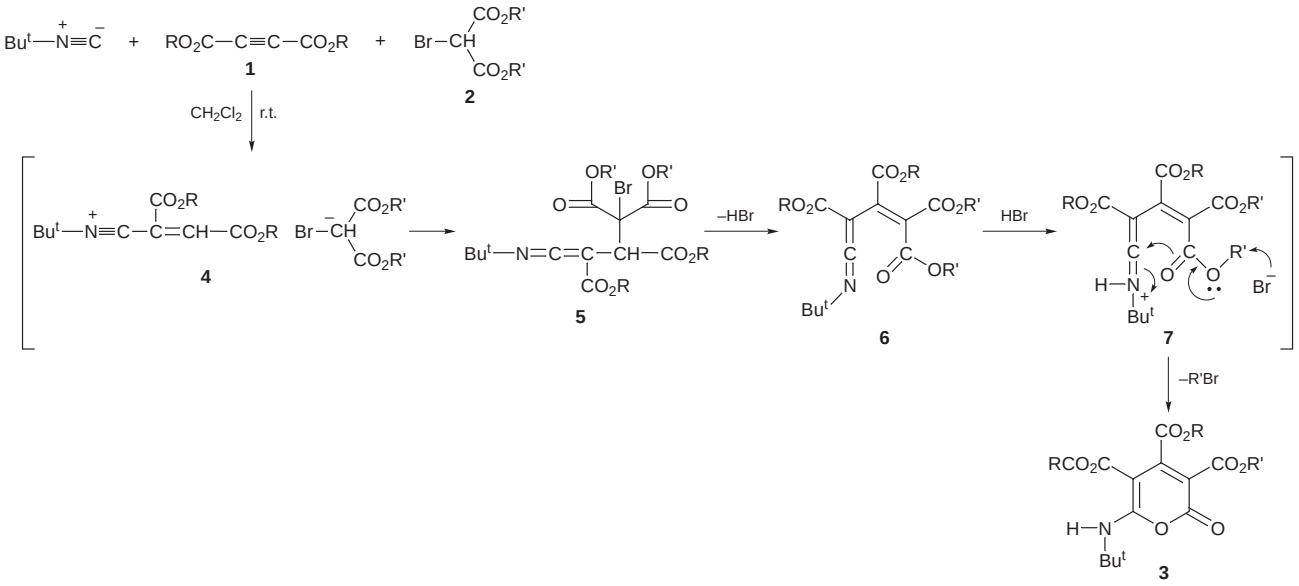
2*H*-Pyran-2-one and its derivatives are important starting materials in the synthesis of cyclobutadienes.[1,2] These heterocycles find use in cycloaddition reactions, providing bicyclolactone adducts which can be elaborated into a variety of highly functionalized cyclohexadienes and benzenes.[3–5] Current synthetic methodology for preparation of this class of compounds still remains fairly specific.[6,7] Here, a direct, efficient and operationally convenient approach to the synthesis of highly functionalized 2*H*-pyran-2-one derivatives **3** using dialkyl 2-bromomalonates **2** is presented. Thus, reaction of *tert*-butyl isocyanide with dialkyl acetylenedicarboxylates **1** in the presence of a strong CH-acid such as **2** leads to the corresponding 2*H*-pyran-2-one derivatives **3** (Scheme 1).



Scheme 1

The three-component condensation reactions produce the hitherto unknown functionalized 2*H*-pyran-2-ones **3** in high yields. The structures of the isolated crystalline compounds **3a**–**d** were deduced from elemental analyses, ^{1}H and ^{13}C NMR spectroscopy. IR spectroscopy was applied to distinguish **3** from the primary product, ketenimine **5** (Scheme 2), which apparently undergoes further transformations to produce the 2*H*-pyran-2-one ring system under the given reaction conditions. Thus, the IR spectra of the isolated products showed strong NH stretching bands at *ca.* 3225–3210 cm^{-1} for alkylamino groups. Further evidence was obtained from proton couple ^{13}C NMR spectra which showed no methine carbon resonance.

The mass spectra of the pyrans **3** are similar, as expected, and confirm their molecular weights. The molecular ion peak is accompanied by a weaker M + 1 peak due to protonation of the pyran molecules in the mass spectrometer. Initial fragmentations involve loss of the side chains and scission of the pyran ring system.



Scheme 2

* To receive any correspondence.

† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

The ^{1}H NMR spectrum of **3a** exhibited four single sharp lines, readily recognizable as arising from *tert*-butyl (δ 1.53) and methoxy (δ 3.79, 3.83 and 3.92) protons, along with a

fairly broad band for the NH group at δ 10.1, indicating extensive intramolecular hydrogen bond formation with the vicinal carbonyl group.

The ^{13}C NMR spectrum of **3a** showed thirteen distinct resonances in agreement with the 2*H*-pyran-2-one structure. Partial assignments of these resonances are given in the Experimental section.

The ^{1}H and ^{13}C NMR spectra of **3b**, **3c** and **3d** are similar to those of **3a**, except for the ester moieties, which exhibited characteristic resonances with appropriate chemical shifts (see Experimental section.).

We have not established a mechanism for the formation of trialkyl 6-*tert*-butylamino-2*H*-pyran-2-one-3,4,5-tricarboxylates **3**, but a reasonable possibility is indicated in Scheme 2. The 2*H*-pyran-2-one **3** apparently results from initial addition of *tert*-butyl isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct, followed by attack of the anion of dialkyl 2-bromomalonate on the positively charged ion to form the ketenimine **5**, which is converted to **3**. The final step of this mechanism involves protonation of the ketenimine moiety of **6** by HBr and dealkylation by the bromide ion. However, an electrocyclic ring closure pathway and protonation of the resultant iminolactone can not be ruled out.

In summary, the reaction of *tert*-butyl isocyanide with electron deficient acetylenic esters in the presence of dialkyl bromomalonates provides a simple one-pot entry into the synthesis of polyfunctional 2*H*-pyran-2-one derivatives.

Experimental

Compounds **1**, **2** and *tert*-butyl isocyanide were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. 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 and 125.77 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

General Procedure for Synthesis of Trialkyl 6-tert-*Butylamino*-2H-*pyran*-2-*one*-3,4,5-*tricarboxylates* **3**.—To a magnetically stirred solution of dialkyl acetylenedicarboxylate (2 mmol) and dialkyl bromomalonate (2 mmol) in dichloromethane (5 ml) was added, dropwise, *tert*-butyl isocyanide (0.17 g, 2 mmol) at room temperature over 2 min. After 3 days the solvent was removed *in vacuo*. The residue was washed with cold diethyl ether (2 × 3 ml), and purified by recrystallization from cold diethyl ether.

3a: light-yellow crystals, mp 163–164 °C, yield 85%; IR (KBr) (ν_{max}/cm^{-1}): 3225 (NH), 1772, 1734, 1708 and 1665 (C=O); δ_H 1.53 (9 H, s, CMe_3), 3.79, 3.83 and 3.92 (9 H, 3 s, 3 OCH_3), 10.1 (1 H, s, NH); δ_C 28.62 (CMe_3), 52.00, 52.40 and 52.50 (3 OCH_3), 54.60 (CMe_3), 83.35 (C-3), 95.81 (C-5), 153.68 (C-4), 155.02 (C-6), 163.78, 164.63, 165.36 and 165.85 (4 C=O). *m/z* 341 (M^+, 5), 342 ($M^+ + 1$, 28), 285 (34), 310 (18), 257 (99), 57 (30%) (Found: C, 51.7: H, 5.6: N, 3.8. $C_{16}H_{21}NO_8$ requires C, 52.78; H, 5.61; N, 4.1%).

3b; light-yellow crystals, mp 133–134 °C, yield 79%; IR (KBr) (ν_{max}/cm^{-1}): 3220 (NH), 1765, 1731, 1692 and 1659 (C=O); δ_H 1.33 (3 H, t, $^{3}J_{HH}$ 7.2 Hz, CH_3), 1.52 (9 H, s, CMe_3), 3.79 and 3.90 (6 H, 2 s, 2 OCH_3), 4.28 (2 H, q, $^{3}J_{HH}$ 7.2 Hz, OCH_2), 10.1 (1 H, s, NH); δ_C 14.01 (CH_2CH_3), 28.82 (CMe_3), 52.52 and 52.61 (2 OCH_3), 54.72 (CMe_3), 61.20 (OCH_2) 85.18 (C-3), 96.87 (C-5), 153.88 (C-4), 154.65 (C-6), 163.44, 164.83, 165.65 and 166.01 (4 C=O). *m/z* 356 (M^++1, 5), 355 (M^+, 28), 310 (15), 299 (34), 271 (99), 57 (100%) (Found: C, 54.0; H, 5.8; N, 4.1. $C_{15}H_{19}NO_8$ requires C, 54.08; H, 5.96; N, 3.94%).

3c: light-yellow crystals, mp 119–121 °C, yield 75%; IR (KBr) (ν_{max}/cm^{-1}): 3215 (NH), 1763, 1730, 1703 and 1671 (C=O); δ_H 1.30 (3 H, t, $^{3}J_{HH}$ 6.9 Hz, CH_3), 1.36 (3 H, t, $^{3}J_{HH}$ 6.9 Hz, CH_3), 1.50 (9 H, s, CMe_3), 3.80 (3 H, s, OCH_3) and 4.24 (2 H, q, $^{3}J_{HH}$ 6.9 Hz, OCH_2), 4.35 (2 H, q, $^{3}J_{HH}$ 6.9 Hz, OCH_2), 10.1 (1 H, s, NH); δ_H 13.81 and 13.99 (2 CH_2CH_3), 28.97 (CMe_3), 52.28 (OCH_3), 54.83 (CMe_3), 61.78 and 61.94 (2 OCH_2) 85.62 (C-3), 96.49 (C-5), 154.22 (C-4), 155.34 (C-6), 164.15, 165.03, 165.44 and 165.49 (4 C=O). *m/z* 370 (M^++1, 5), 369 (M^+, 45), 338 (8), 324 (10), 313 (27), 285 (100), 57 (5%) (Found: C, 54.9; H, 6.3; N, 3.9. $C_{17}H_{23}NO_8$ requires C, 55.28; H, 6.28; N, 3.79%).

3d: light-yellow crystals, mp 116–117 °C, yield 75%; IR (KBr) (ν_{max}/cm^{-1}): 3210 (NH), 1752, 1740, 1706 and 1661 (C=O); δ_H 1.30 (3 H, t, $^{3}J_{HH}$ 6.9 Hz, CH_3), 1.32 (3 H, t, $^{3}J_{HH}$ 6.9 Hz, CH_3), 1.36 (3 H, t, $^{3}J_{HH}$ 6.9 Hz, CH_3), 1.50 (9 H, s, CMe_3), 3.80 (3 H, s, OCH_3) and 4.24 (2 H, q, $^{3}J_{HH}$ 6.9 Hz, OCH_2), 4.35 (2 H, q, $^{3}J_{HH}$ 6.9 Hz, OCH_3), 10.1 (1 H, s, NH): δ_C 13.79, 14.01 and 14.19 (3 CH_2CH_3), 29.00 (CMe_3) 54.78 (CMe_3), 61.32, 61.73 and 61.91 (3 OCH_2) 85.34 (C-3), 97.30 (C-5), 154.22 (C-4), 154.27 (C-6), 163.69, 165.00, 165.25 and 165.52 (4 C=O). *m/z* 384 ($M^+ + 1$, 8), 383 (M^+, 40), 338 (15), 327 (32), (100), 57 (5%) (Found: C, 56.4; H, 6.6; N, 3.8. $C_{18}H_{25}NO_8$ requires C, 56.39; H, 6.57; N, 3.65%).

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