SHORT PAPER

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The reaction between tert-butyl isocyanide and acetylenic esters in presence of 2-thenoyltrifluoroacetone: a synthesis of highly functionalised 4*H*-pyrans†

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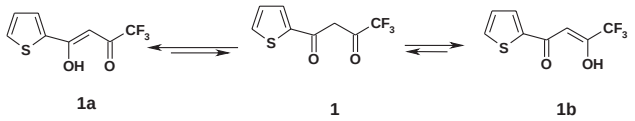
Tert-butyl isocyanide reacts with dialkyl acetylenedicarboxylates in the presence of 2-thenoyltrifluoroacetone to yield 4*H*-pyran derivatives in good yields.

Keywords: *t*-butyl isocyanide, acetylenic esters, β-diketones, 4*H*-pyrans

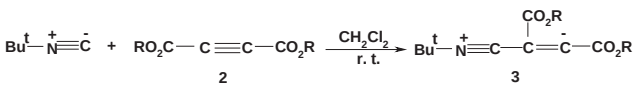
Controlling the chemoselectivity aspects of reaction has always been a prime challenge to synthetic organic chemistry.[1] These concerns are especially pressing when the preparations of multifunctional substances, or of those with specific biological action, are involved. 4*H*-pyran and its derivatives are important heterocyclic compounds for which current synthetic methodology for their preparation of this class of compounds still remains fairly specific. Here, a direct, efficient and operationally convenient approach to the synthesis of highly functionalised 4*H*-pyran derivatives (**5**) using 2-thenoyltrifluoroacetone (**1**) is presented.

2-Thenoyltrifluoroacetone **1** is a multifunctional system, to a large extent enolized in the liquid phase. It has two enolic tautomers, as indicated by ^{1}H and ^{13}C NMR spectroscopy. As part of our current studies on the development of new routes to heterocyclic systems[2], we report a chemoselective route to the synthesis of 4*H*-pyran derivatives using the reaction of *tert*-butyl isocyanide and acetylenic esters in the presence of 2-thenoyltrifluoroactone.



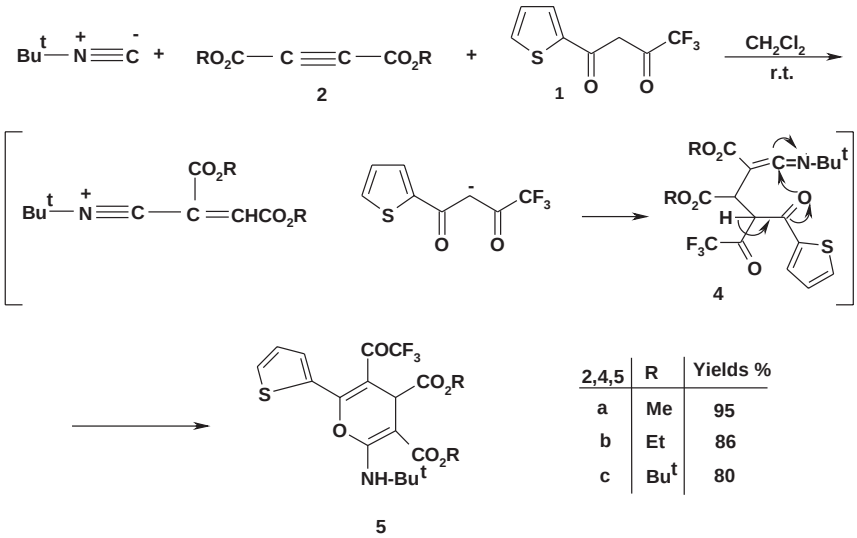
1a **1** **1b**

The reaction of alkyl isocyanides such as tert-butyl isocyanide with carbon-centered triple bonds tends to occur in a stepwise manner through a zwitterionic intermediate, the ultimate fate of which appears to be dictated by the nature of the original triple-bonded substrate.[3-5] In the case of electron-deficient acetylenic esters (**2**), it is reasonable to assume the prior formation of a 1 : 1 intermediate (**3**) which possesses predominantly carbanionic character.



2 **3**

Already, the reactive intermediate **3** has been trapped by *N*,*N*′-dimethylbarbituric acid.[6] The work reported here was undertaken in order to study the possibility of trapping the reactive 1:1 intermediate **3** using 2-thenoyltrifluoroacetone (**1**) as an OH-acid. We find that *tert*-butyl isocyanide and dialkyl acetylenedicarboxylates (**2**) in the presence of 2-thenoyltrifluoroacetone undergo a smooth 1 : 1 : 1 addition reaction in dichloromethane at room temperature to produce the hitherto unknown dialkyl 2-(*t*-butylamino)-6-(2-thenoyl)-5-(2,2,2-trifluoroacetyl)-4*H*-pyran-3,4-dicarboxylates **5a–c**. On the basis of the well established chemistry of isocyanides[3-5] it is



2,4,5	R	Yields %
a	Me	95
b	Et	86
c	Bu^t	80

5

Scheme 1 Formation of the 4*H*-pyrans (5a–c).

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

reasonable to assume that compounds **5** result from initial addition of the *t*-butyl isocyanide to the acetylenic ester and concomitant protonation of the 1 : 1 adduct by the 2-thenoyltrifluoroacetone. The positively charged nitrilium intermediate is attacked by the enolate anion (**1a**) to form ketenimines **4.** Such addition products apparently isomerise, under the reaction conditions, to produce the biheterocyclic system **5** (Scheme 1). Structure **5** was assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H, ^{13}C NMR spectral data.

The ^{1}H NMR spectrum of compound **5a** exhibited four single sharp lines, readily recognizable as arising from *tert*-butyl(δ 1.43), methoxy (δ 3.70 and 3.72) and methine (δ 4.56) protons, along with a fairly broad band for the NH group at δ 8.75, indicating extensive intramolecular hydrogen bond formation with the vicinal ester carbonyl group.[7] The aromatic(thiophene) protons appear as three doublets of doublets at δ 7.08 ($^3J_{HH}$ = 5.3 and 3.5 Hz), 7.29 ($^3J_{HH}$ = 3.5 and $^4J_{HH}$ = 0.7 Hz)and 7.63 ($^3J_{HH}$ = 5.3 and $^4J_{HH}$ =0.7 Hz). The ^{13}C NMR spectrum showed seventeen distinct resonances cosistent with the assigned dimethyl 2-(t-butylamino)-6-(2-thenoyl)-5-(2,2,2-trifluoroacetyl)-4*H*-pyrane-3,4-dicarboxylate structure. The ^{1}H and ^{13}C NMR spectra of **5b** and **5c** are similar to those of **5a**, except for the ester residues, which displayed characteristic resonances with appropriate chemical shifts (see experimental section).

The structural assignments of compounds **5a–c** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest are the strong carbonyl absorption bands at 1650–1753 cm^{-1} for all compounds, and a fairly broad NH peak at about 3520–3590 cm^{-1} for the *t*-butylamino group.

The procedure that we have described here represents an acceptable method for the preparation of polyfunctional 4*H*-pyrans of potential synthetic interest.

Experimental

Dialkyl acetylenedicarboxylates, *t*-butyl isocyanide and 2-thenoyl trifluoroacetone were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. ^{1}H and ^{13}CNMR spectra were measured with a Bruker DRX-500 Avance spectrometer at 500 and 125.8 MHz, respectively. IR spectra were recorded using a Shimadzu IR-470 spectrometer.

General procedure for synthesis of dialkyl 2-(t-butylamino)-6-(2-thenoyl)-5-(2,2,2-trifluoroacetyl)-4H-pyran-3,4-dicarboxylate (**5a–c**): To a magnetically stirred solution of 2-thenoyltrifluoroacetone (0.44 g, 2 mmol) and dialkyl acetylenedicarboxylate (2 mmol) in CH_2Cl_2 (8 ml) was added, dropwise, a mixture of *t*-butyl isocyanide (0.22 ml, 2 mmol) in CH_2Cl_2 (2 ml) at –10 ºC over 10 min. The mixture was allowed to warm to room temperature and stirred for 48 h. The solvent was removed under reduced pressure and the product was purified by recrystallisation from ether-chloroform.

Dimethyl ester (**5a**): Lemon-yellow crystals, m.p. 127 ºC, yield 0.85 g (95%); IR (KBr) (ν_{max}, cm^{-1}): 1700, 1728 and 1753 (C=O), 3440–3590 (NH); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.43 (9 H, s, C*Me*$_3$), 3.7 and 3.72 (6 H, 2 s, 2 OCH_3), 4.56 (1 H, s, CH), 7.08 (1 H, dd, $^3J_{HH}$= 5.3 and 3.5 Hz, CH thiophene), 7.29 (1 H, dd, $^3J_{HH}$= 3.5 and $^4J_{HH}$= 0.7 Hz, CH thiophene), 7.63 (1 H, dd, $^3J_{HH}$= 5.3 and $^4J_{HH}$= 0.7 Hz, CH thiophene), 8.75 (1 H, br s, NH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ_C 30.46 (C*Me*$_3$), 40.0 (CH), 51.24 and 52.6 (2 OCH_3), 52.8 (*C*Me$_3$), 71.7 and 109.5 (2 *^{13}C*=C-O), 115.44 (q, $^1J_{CF}$ = 291.8 Hz, CF_3), 127.5, 131.5, 132.8 and 133.2 (4 C thiophene), 151.32 and 160.0 (2 C=*^{13}C*-O), 169.1 and 172.0 (2 C=O, *C*$O_2$$CH_3$), 184.9 (q, $^2J_{CF}$ = 36.5 Hz, *C*OCF_3). (Found: C, 51.2; H, 4.53; N, 3.16. $C_{19}H_{20}F_3NO_6S$ requires C, 51.01; H, 4.51; N, 3.13 %).

Diethyl ester (**5b**): Lemon-yellow crystals, m.p. 120 ºC, yield 0.82 g (86%); IR (KBr) (ν_{max}, cm^{-1}): 1700, 1718 and 1743 (C=O), 3400–3550 (NH); ^{1}H NMR (500 MHz, $CDCl_3$); δ_H 1.23 and 1.26 (6 H, 2 t, $^3J_{HH}$=7.1 Hz, 2 CH_3), 1.42 (9 H, s, C*Me*$_3$), 4.13 and 4.20 (4 H, 2 q, $^3J_{HH}$= 7.1 Hz, 2 OCH_2), 4.53 (1 H, s, CH), 7.07 (1 H, dd, $^3J_{HH}$= 4.5 and 3.2 Hz, CH thiophene), 7.27 (1 H, $^3J_{HH}$= 3.2 Hz and $^4J_{HH}$= 0.9 Hz, CH thiophene), 7.61 (1 H, dd, $^3J_{HH}$ = 4.5 Hz and $^4J_{HH}$ = 0.9 Hz, CH thiophene), 8.73 (1 H, br s, NH); ^{13}C NMR(125.77 MHz, $CDCl_3$): δ_C 14 and 14.4 (2 CH_3), 30.46 (C*Me*$_3$), 40.1 (CH), 52.27 (*C*Me$_3$), 59.7 and 61.5 (2 OCH_2), 72 and 109.5 (2 *^{13}C*=C-O), 115.47 (q, $^1J_{CF}$ =291.8 Hz, CF_3), 127.42, 131.37, 132.87 and 133.12 (4 C thiophene), 151.37 and 159.9 (2 C=*^{13}C*-O), 168.7 and 171.68 (2 C=O, *C*O_2Et), 184.97 (q, $^2J_{CF}$= 36.5 Hz, *C*OCF_3). (Found: C, 53.2; H, 5.2 N, 2.98. $C_{21}H_{24}F_3NO_6S$ requires C, 53.05; H, 5.09; N, 2.95 %).

Di-t-butyl ester (**5c**): Lemon-yellow crystals, m.p. 110 ºC, yield 0.85 g (80%); IR (KBr) (ν_{max}, cm^{-1}): 1650, 1690 and 1753 (C=O), 3420–3560 (NH); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.42, 1.43 and 1.48 (27 H, 3 s, 3 CMe_3), 4.34 (1 H, s, CH), 7.05 (1 H, dd, $^3J_{HH}$=5.3 and 3.8 Hz, CH thiophene), 7.31 (1 H, dd, $^3J_{HH}$ = 3.8 and $^4J_{HH}$ = 0.9 Hz, CH thiophene), 7.58 (1 H, dd, $^3J_{HH}$ = 5.3 and $^4J_{HH}$ = 0.9 Hz, CH thiophene), 8.65 (1 H, br s, NH); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ_C 27.9, 28.5 and 30.5 (3 C*Me*$_3$), 41.12 (CH), 52.5 (NH*C*Me$_3$), 79.8 and 81.7 (2 CO_2*C*Me$_3$), 73.4 and 109.8 (2 *^{13}C*=C-O), 115.6 (q, $^1J_{CF}$ = 292.3 Hz, CF_3), 127.3, 130.8, 132.93 and 132.93 (4 C thiophene), 151 and 159.6 (2 C=*^{13}C*-O), 168.4 and 170.7 (2 C=O, *C*O_2CMe$_3$), 184.3 (q, $^2J_{CF}$ = 36.2 Hz, *C*OCF_3). (Found: C, 56.6; H, 6.15; N, 2.68 $C_{25}H_{32}F_3NO_6S$ requires C, 56.49; H, 6.07; N, 2.63 %).

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