Chemoselective synthesis of dialkyl 2-(*tert*-butylamino)-6-methyl-5-trifluoroacetyl-4*H*-pyran-3,4-dicarboxylates

S. Asghari, M. Zaty, and S. Safiri*

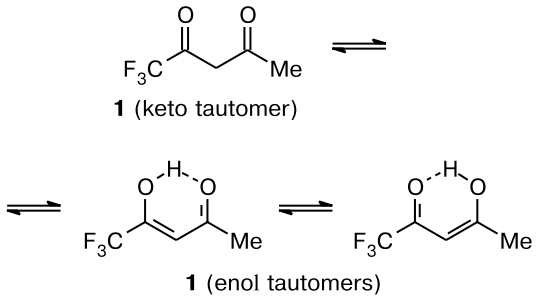
Department of Chemistry, Mazandaran University, Babolsar, Iran.
E-mail: asgharis@umz.ac.ir

The reaction of *tert*-butyl isocyanide with dialkyl acetylenedicarboxylate affords a highly reactive 1 : 1 intermediate which can be trapped by 1,1,1-trifluoropentane-2,4-dione.

Key words: isocyanides, 4*H*-pyrans, 1,1,1-trifluoropentane-2,4-dione.

Chemoselective reactions have always been a prime challenge to organic chemists,[1] especially for the preparation of multifunctional substances of specific biological action. The reaction of *tert*-butyl isocyanide with a triple carbon—carbon bond tends to occur in a stepwise manner *via* a zwitterionic intermediate, fate of which appears to be dictated by the nature of the original acetylenic compound.[2—6] In this work, we present a direct, efficient, and operationally convenient approach to the chemoselective synthesis of polyfunctionalized 4*H*-pyrans using a strong CH acid. 1,1,1-Trifluoropentane-2,4-dione (**1**) is a β-diketone with a strong electron-withdrawing CF_3 group; therefore, it can be such a strong CH acid (or OH acid in the form of an enol tautomer). The ^{1}H NMR spectrum of compound **1** shows a broad signal at δ ~14 that corresponds to the enol tautomer (Scheme 1).

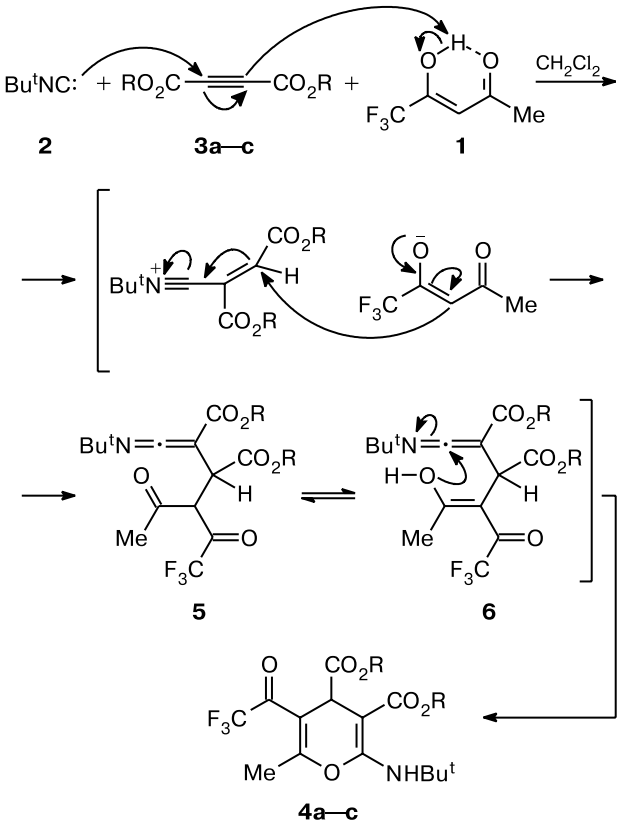
Scheme 1



Results and Discussion

tert-Butyl isocyanide (**2**) smoothly reacts with dialkyl acetylenedicarboxylates **3a—c** in the presence of 1,1,1-trifluoropentane-2,4-dione (**1**) in CH_2Cl_2 at room temperature to give [1 : 1 : 1] addition products, the polyfunctionalized 4*H*-pyrans **4a—c** (Scheme 2).

Scheme 2



	R	Yield (%)
a	Me	92
b	Et	85
c	Bu^t	83

On the basis of the well established chemistry of isocyanides,[2,3] it is reasonable to assume that compounds **4a—c** result from the initial addition of *tert*-butyl isocyanide (**2**) to acetylenic ester **3** and concomitant protona-

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tion of the 1 : 1 adduct by 1,1,1-trifluoropentane-2,4-dione (**1**). The enolate anion of the CH acid attacks the positively charged ion and forms keteneimine **5**. Then keteneimine **5** isomerizes under the reaction conditions to produce enol tautomer **6**. The latter attacks the sp-hybridized C atom of the keteneimine moiety, then the proton transfer occurs, and pyran derivatives are formed (see Scheme 2).

The structures of compounds **4a—c** were established on the basis of their IR and ^{1}H, ^{13}C NMR spectra. Although the presence of the ^{19}F nuclei complicates both the ^{1}H and ^{13}C NMR spectra, it helps in assignment of the signals due to coupling with ^{1}H and ^{13}C nuclei.

The ^{1}H NMR spectrum of compound **4a** exhibits six singlets, readily recognizable as arising from *tert*-butyl (δ 1.36), methyl (δ 2.30), methoxy (δ 3.60 and 3.68), and methine (δ 4.58) protons, along with a fairly broad band for the NH group at δ 8.46, indicating extensive intramolecular hydrogen bond formation with the vicinal carbonyl group.[7]

The ^{13}C NMR spectrum of compound **4a** shows fourteen distinct lines consistent with the dimethyl 2-(*tert*-butylamino)-6-methyl-5-trifluoroacetyl-4*H*-pyran-3,4-dicarboxylate structure. The ^{1}H and ^{13}C NMR spectra of compounds **4b**,**c** are similar to those of product **4a**, except for the ester groups, which display characteristic resonances with appropriate chemical shifts (see Experimental).

The IR spectra of compounds **4a—c** were used to distinguish them from the primary products, keteneimine derivatives **5**. Of special interest are the strong carbonyl absorption bands at 1660—1735 cm^{-1} for all compounds and a fairly broad NH peak at ~3150—3180 cm^{-1} for the alkylamino group (see Experimental).

Experimental

Reagents were obtained from Fluka (Switzerland) and used without further purification. IR spectra were recorded on a UNICAM IR-1100 spectrometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on a Bruker DRX-500 AVANCE spectrometer at 500, 125.8, and 470.59 MHz, respectively.

Dimethyl 2-(*tert*-butylamino)-6-methyl-5-trifluoroacetyl-4*H*-pyran-3,4-dicarboxylate (4a). A solution of *tert*-butyl isocyanide (**2**) (0.166 g, 2 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a magnetically stirred solution of 1,1,1-trifluoropentane-2,4-dione (**1**) (0.308 g, 2 mmol) and dimethyl acetylenedicarboxylate (**3a**) (0.282 g, 2 mmol) in CH_2Cl_2 (5 mL) at −10 °C over 10 min. The mixture was allowed to warm to ~20 °C and left for 3 days. The solvent was removed under reduced pressure, and the residue was purified by silica gel (Merck, 230—400 mesh) column chromatography using a hexane—AcOEt (10 : 1) mixture as an eluent. The solvent was removed under reduced pressure to give product **4a** (0.676 g, 92%) as a green viscous oil. Found (%): C, 50.10; H, 5.25; N, 3.62. $C_{16}H_{20}F_3NO_6$. Calculated (%): C, 50.66; H, 5.31; N, 3.69. IR (KBr), ν/cm^{-1}: 3180 (NH); 1735, 1667 (C=O). ^{1}H NMR ($CDCl_3$), δ: 1.36 (s, 9 H, CMe_3); 2.30 (s, 3 H, Me); 3.60, 3.68 (both s, 6 H, OMe); 4.58 (s, 1 H, CH); 8.46 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 18.88 (Me); 30.37 (CMe_3); 36.63 (q, CH, $^4J_{F,C}$ = 3.0 Hz); 51.14, 52.42 (OMe); 52.66 ($NCMe_3$); 72.11, 108.92 (C=C—O); 116.08 (q, CF_3, $^1J_{F,C}$ = 291.9 Hz); 159.80, 162.16 (C=C—O); 169.00, 172.20 (CO_2R); 181.60 (q, C(O)CF_3, $^2J_{F,C}$ = 35.0 Hz). ^{19}F NMR ($CDCl_3$), δ: −65.05.

Diethyl 2-(*tert*-butylamino)-6-methyl-5-trifluoroacetyl-4*H*-pyran-3,4-dicarboxylate (4b) was synthesized similarly to compound **4a** as a green oil. The yield was 0.691 g (85%). Found (%): C, 52.78; H, 5.90; N, 3.37. $C_{18}H_{24}F_3NO_6$. Calculated (%): C, 53.07; H, 5.94; N, 3.44. IR (KBr), ν/cm^{-1}: 3150 (NH); 1732, 1679 (C=O). ^{1}H NMR ($CDCl_3$), δ: 1.11, 1.18 (both t, 6 H, Me, ^3J = 7.2 Hz); 1.31 (s, 9 H, CMe_3); 2.46 (s, 3 H, Me); 3.94—4.17 (m, 4 H, OCH_2); 4.52 (s, 1 H, CH); 8.41 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 13.88, 14.39 (Me); 18.83 (Me); 30.37 (CMe_3); 36.80 (q, CH, $^4J_{F,C}$ = 2.8 Hz); 52.59 ($NCMe_3$); 59.65, 61.32 (OCH_2); 72.29, 108.93 (C=C—O); 116.07 (q, CF_3, $^1J_{F,C}$ = 291.9 Hz); 159.54, 161.93 (C=C—O); 168.61, 171.76 (CO_2R); 181.34 (q, C(O)CF_3, $^2J_{F,C}$ = 35.3 Hz). ^{19}F NMR ($CDCl_3$), δ: −65.15.

Di-*tert*-butyl 2-(*tert*-butylamino)-6-methyl-5-trifluoroacetyl-4*H*-pyran-3,4-dicarboxylate (4c) was synthesized similarly to compound **4a** as a green oil. Found (%): C, 56.54; H, 6.80; N, 2.95. $C_{22}H_{32}F_3NO_6$. Calculated (%): C, 57.01; H, 6.96; N, 3.02. IR (KBr), ν/cm^{-1}: 3170 (NH); 1725, 1673 (C=O). ^{1}H NMR ($CDCl_3$), δ: 1.36 (s, 9 H, CMe_3); 1.44, 1.47 (both s, 18 H, CMe_3); 2.26 (s, 3 H, Me); 4.41 (s, 1 H, CH); 8.35 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 18.58 (Me); 27.81, 28.34, 30.49 (CMe_3); 38.17 (q, CH, $^4J_{F,C}$ = 2.9 Hz); 52.33 ($NCMe_3$); 73.79 (C=C—O); 79.50, 81.57 ($OCMe_3$); 109.21 (C=C—O); 118.73 (q, CF_3, $^1J_{F,C}$ = 292.0 Hz); 159.32, 161.14 (C=C—O); 168.25, 170.84 (CO_2R); 181.74 (q, C(O)CF_3, $^2J_{F,C}$ = 35.0 Hz). ^{19}F NMR ($CDCl_3$), δ: −64.56.

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