Reaction between nitrogen–containing heterocycles and dialkyl acetylenedicarboxylate with strong CH-acid: synthesis of stable highly functionalised 1,4-diionic nitrogen betaines

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Protonation of highly reactive 1,4-zwitterionic intermediate generated in the reaction between pyridine or isoquinoline and dialkyl acetylenedicarboxylates by strong CH-acid such as 1,1,1,5,5,5-hexafluoropentane-2,4-dione, leads to a vinyl pyridinium cation derivatives, which undergo carbon centred Michael type addition with the conjugate base of the CH-acid to produce highly functionalised stable 1,4-diionic nitrogen betaines.

Keywords: 1,1,1,5,5,5-hexafluoropentane-2,4-dione, pyridine; CH-acid, isoquinoline, zwitterionic intermediate, 1,4-diionic nitrogen betaines

The pronounced reactivity of nitrogen–containing heterocycles towards electron-deficient acetylenic compounds such as dimethyl acetylenedicarboxylate (DMAD) is well documented.[1] The reaction generally involves the initial addition of pyridine to DMAD to form the 1,4-zwitterionic intermediate, which undergoes further reaction with DMAD leading to quinazoline derivatives or it can be trapped by various electrophiles.[2-8] Also the reactions of pyridine and DMAD have been studied in the presence of a CH-acid such as dimethyl malonate and ethyl cyanoacetate. In the case of dimethyl malonate the malonate cyclohepta-1,3-diene derivatives were obtained,[9] however the reaction of DMAD with ethyl cyanoacetate in the presence of pyridine took a different course.[10]

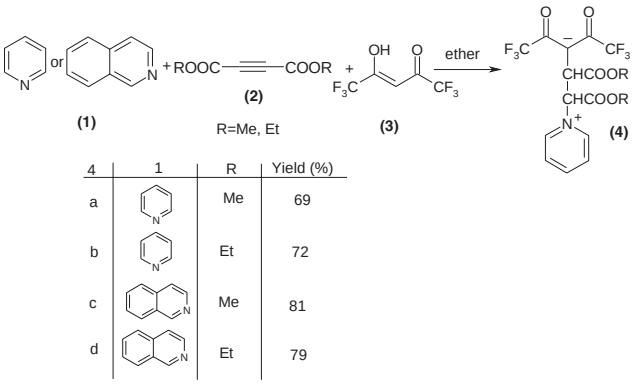
In a continuation of our previous work on the chemistry of 1,1,1,5,5,5-hexafluoropentane-2,4-dione,[11-13] with the purpose of preparing 1,4-diionic nitrogen betaines bearing trifluoromethyl substituent, we performed the reaction of pyridine or isoquinoline and dialkyl acetylenedicarboxylates in the presence of 1,1,1,5,5,5-hexafluoropentane-2,4-dione.

Results and discussion

A mixture of pyridine or isoquinoline **(1)** and dialkyl acetylenedicarboxylates **(2)** when treated with 1,1,1,5,5,5-hexafluoropentane-2,4-dione **(3)** at room temperature in diethyl ether for 10 hours affords the 1,4-diionic nitrogen betaines **(4)** in 69–81 % yields. (Scheme 1) Compounds **4a–4d** are stable solids whose structures are fully supported by IR, high-field ^{1}H, ^{13}C and ^{19}F NMR spectroscopy and mass spectrometric data. The mass spectra of these 1:1:1 adducts exhibited fairly weak molecular ion peaks.

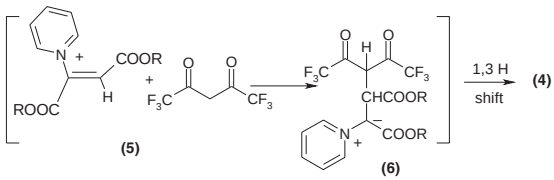
On the basis of the well established chemistry of nitrogen heterocycle nucleophiles,[14] it is reasonable to assume that betaines **4** result from the initial addition of pyridine or isoquinoline to the electron deficient acetylenic ester and subsequent protonation of the 1:1 adduct by 1,1,1,5,5,5-hexafluoropentane-2,4-dione. Then, the vinyl pyridinium cation **5** is attacked by the enolate anion of the CH-acid to generate the nitrogen ylide **6**, which isomerises under the reaction conditions to produce the 1,4-diionic compounds **4** (Scheme 2).

The 500 MHz ^{1}H NMR spectra of compound **4a** displayed signals for vicinal methine protons at δ 4.48 and 6.38 which appear as two sets of doublets with $^3J_{HH}$ values of 7.90 Hz and 7.92, respectively. The two trifluoromethyl groups are homotopic and show a signal in the ^{19}F and ^{13}C NMR spectra.

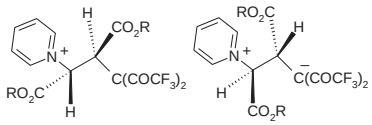


4	1	R	Yield (%)
a		Me	69
b		Et	72
c		Me	81
d		Et	79

Scheme 1



Scheme 2



Scheme 3

Also compound **4** has two stereogenic centers, and therefore two diastereomers are expected (Scheme 3). The ^{1}H NMR spectra of the crude reaction mixtures obtained from **4a–4d** were consistent with the presence of only one diastereomer.

In conclusion, we have found that the reaction of pyridine or isoquinoline with electron deficient dialkyl acetylene-dicarboxylates in the presence of a strong CH-acid such as 1,1,1,5,5,5-hexafluoropentane-2,4-dione leads to a facile synthesis of the highly functionalized 1,4-diionic nitrogen betaines **4a–4d** in fairly good yields. The present method carries the advantage that the reaction is performed under mild conditions and the substrates can be mixed without any activations and modifications.

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Experimental

All melting points are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.13, 125.77 and 470.56 MHz in DMSO-d_6 or acetone-d_6 using TMS or $CFCl_3$ as internal standard. The chemicals used in this work were purchased from Aldrich chemical company.

Typical procedure for the preparation of dimethyl 2-(1,1,1,5,5,5-hexafluoro-2,4-dioxo-pentane-3-yl-3-yide)-3-pyridinium-1,4-butanedioate (**4a**): To a magnetically stirred solution of 1,1,1,5,5,5 -hexafluoropentane-2,4-dione (0.43 g, 2 mmol) and dimethyl acetylenedicarboxylate (0.28 g, 2 mmol) in diethyl ether (10 ml) was added dropwise a mixture of pyridine (0.16 g, 2 mmol) in diethyl ether (5 ml) at room temperature (25 °C). After 10 h the precipitate was filtered and washed with cold diethyl ether (10 ml) and ethyl acetate (5 ml), to yield **4a** as a white powder (0.59 g, yield 69%). m.p. 159–160 °C. ν_{max}/cm^{-1} (KBr): 1735, 1625, 1529, 1492. ^{1}H NMR (DMSO-d_6): δ_H 3.57 and 3.77 (6H, 2s, $2OCH_3$), 4.48 (1H, d, $^{3}J_{HH}$ 7.90 Hz, CH), 6.38 (1H, d, $^{3}J_{HH}$ 7.92 Hz, CH-N^+), 8.09 (2H, m, H-3,5 of py), 8.63 (1H, t, $^{3}J_{HH}$ 7.76 Hz, H-4 of py), 8.76 (1H, d, , $^{3}J_{HH}$ 5.91 Hz, H-2,6 of py); ^{13}C NMR (DMSO-d_6): 46.42 (CH), 52.47 and 53.81 ($2OCH_3$), 69.46 (CH-N^+), 95.15 [C(CO)2], 117.83 (q, $^{1}J_{CF}$ 289.25 Hz, $2CF_3$), 127.36, 145.69 and 147.19 (py), 167.47 and 171.58 ($2CO_2Me$), 172.73 (m, $2COCF_3$); ^{19}F NMR (DMSO-d_6): δ_F –70.81 ($2CF_3$)**;** MS (m/z, %) 411 (M^+-H_2O, 5), 351 (M^+-py, 7), 291 (22), 249 (51), 163 (28),79 (93), 59 (100).

Selected data for **4b:** White powder (0.66 g, yield 72%). m.p. 142–144 °C. ν_{max}/cm^{-1} (KBr): 1737, 1636, 1523, 1457. ^{1}H NMR (DMSO-d_6): δ_H 1.07 (3H, t, $^{3}J_{HH}$ 7.02 Hz, CH_3), 1.20 (3H, t, $^{3}J_{HH}$ 7.04 Hz, CH_3), 4.01–4.27 (4H, m, OCH_2), 4.48 (1H, d, $^{3}J_{HH}$ 8.02 Hz, CH), 6.35 (1H, d, $^{3}J_{HH}$ 8.01 Hz, CH-N^+), 8.10 (2H, m, H-3,5 of py), 8.63 (1H, t, $^{3}J_{HH}$ 7.68 Hz, H-4 of py), 8.75 (1H, d, $^{3}J_{HH}$ 5.99 Hz, H-2,6 of py); ^{13}C NMR (DMSO-d_6): 13.61 and 13.78 ($2CH_3$), 46.64 (CH), 60.91 and 62.91 ($2OCH_2$), 69.68 (CH-N^+), 95.31 [*C*(CO)2], 117.84 (q, $^{1}J_{CF}$ 288.75 Hz, $2CF_3$), 127.39, 145.58 and 147.12 (py), 166.96 and 170.92 ($2CO_2Et$), 172.64 (m, $2COCF_3$); ^{19}F NMR (DMSO-d_6): δ_F –70.86 ($2CF_3$)**.** MS (*m/z*, %) 377 (M^+-py, 5), 333 (15), 305 (19), 287 (20), 235 (100), 163 (48), 79 (76), 52 (78).

Selected data for **4c:** Yellow powder (0.78 g, yield 81%). m.p. 150–151 °C. ν_{max}/cm^{-1} (KBr): 1732, 1638, 1520, 1456. ^{1}H NMR (acetone-d_6): δ_H 3.63 and 3.86 (6H, 2s, $2OCH_3$), 4.78 (1H, d, $^{3}J_{HH}$ 8.01 Hz, CH), 6.51 (1H, d, $^{3}J_{HH}$ 8.01 Hz, CH-N^+), 8.11–8.61 (1H, m, Ar). ^{13}C NMR (acetone-d_6): 46.96 (CH), 51.37 and 52.80 ($2OCH_3$), 69.83 (CH-N^+), 95.04 [*C*(CO)2], 117.32 (q, $^{1}J_{CF}$ 287.13 Hz, $2CF_3$), 124.66, 126.61, 126.81, 130.48, 131.01, 134.55, 137.49, 137.62 and 150.49 (Ar), 167.39 and 171.65 ($2CO_2Me$), 172.52 (m, $2COCF_3$). ^{19}F NMR (acetone-d_6): δ_F –72.31. MS (*m/z*, %) 480 (M^++1, 8), 449 (6), 387 (10), 287 (35), 249 (69), 129 (100), 59 (96).

Selected data for **4d:** Yellow powder (0.80 g, yield .79%). m.p. 146–147 °C. ν_{max}/cm^{-1} (KBr): 1744, 1713, 1625, 1562. ^{1}H NMR (acetone-d_6): δ_H 1.15 (3H, t, $^{3}J_{HH}$ 7.02 Hz, CH_3), 1.28 (3H, t, $^{3}J_{HH}$ 7.12 Hz, CH_3), 4.06–4.39 (4H, m, OCH_2), 4.78 (1H, d, $^{3}J_{HH}$ 8.15 Hz, CH), 6.48 (1H, d, $^{3}J_{HH}$ 8.15 Hz, CH-N^+), 8.11–8.61 (7H, m, Ar). ^{13}C NMR (acetone-d_6): 13.78 and 13.96 ($2CH_3$), 48.18 (CH), 61.48 and 63.51 ($2OCH_2$), 71.15 (CH-N^+), 96.36 [*C*(CO)2], 118.78 (q, $^{1}J_{CF}$ 288.63 Hz, $2CF_3$), 125.74, 127.68, 127.89, 131.53, 132.01, 135.50, 138.53, 138.66 and 151.55 (Ar), 167.96 and 172.01 ($2CO_2Et$), 173.97 and 174.21 (2m, $COCF_3$). ^{19}F NMR (acetone-d_6): δ_F –72.35. MS (*m/z*, %) 508 (M^++1, 7), 379 (26), 333 (21), 287 (27), 129 (100), 69 (35).

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