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Regiospecific [2+2] cycloadditions of electron-poor acetylenes to (*Z*)-2-acylamino-3-dimethylaminopropenoates: synthesis of highly functionalised buta-1,3-dienes

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Abstract

Microwave-assisted [2+2] cycloaddition reactions of 2-amino-3-dimethylaminopropenoates with acetylenecarboxylates furnished highly functionalised 1-amino-4-(dimethylamino)buta-1,3-dienes in 40–94% yields. All reactions were observed to consistently produce single geometrical isomers, and in cases where non-symmetrical acetylenes were employed the reactions proceeded in a regiospecific manner.

Keywords: Regiospecific [2+2] cycloadditions; (*Z*)-2-Acylamino-3-dimethylaminopropenoates; Acetylenecarboxylates; Highly functionalised buta-1,3-dienes; Microwave irradiation

In the last few decades there have been some reports of reactions of simple tertiary enamines with electron-poor acetylenes, such as alkyl propiolates and dialkyl acetylenedicarboxylates.[1a–d] It has been generally accepted that these reactions initially proceed by a [2+2] cycloaddition. However, the structure of the final product is strongly dependant on the structure of the starting compound and reaction conditions.[1d] The geometry of the obtained products was, in some cases, unambiguously determined by Reinhoudt et al. in the early 1980s.[1d] When these reactions were extended to other functionalised enamines and enaminones, in some cases, a Michael type addition took place preferentially over the [2+2] cycloaddition.[2a–c]

Despite the fact that reactions of electron-poor acetylenes have been performed with many different enaminones, until now no study has been undertaken on the reactions of 2-acylamino-3-dimethylaminopropenoates with electron-deficient acetylenes. The wide applicability of 3-dimethylaminopropenoates in the synthesis of heterocyclic systems has encouraged us to study their reactions with acetylenes.

3-Dimethylaminopropenoates and related enaminones have been demonstrated to be useful reagents in heterocyclic synthesis,[3a–e] including the preparation of natural products and their analogues, such as aplysinopsins,[4a,b] meridinanines[5a,b] and dipodazines.[6a–c]

In this connection, we recently reported an efficient method for the preparation and functionalisation of highly substituted 1-aminopyrroline, 1-aminopyrrole and oxazoline–pyrroline fused systems from 1,2-diaza-1,3-butadienes and 3-dimethylaminopropenoates,[7] and the regio- and stereoselective one-pot synthesis of oxazoline-fused pyridazine via a 'Michael addition–pyridazine cyclisation–oxazoline cyclisation' cascade reaction.[8]

When methyl (*Z*)-2-acylamino-3-(dimethylamino)propenoates **1** and electron-poor acetylenes **2** were heated in acetonitrile under microwave irradiation, the corresponding (1*E*,3*E*)-1-acylamino-4-(dimethylamino)buta-1,3-dienes **3a**–**i** were isolated as the only isomers in 40–94% yields (Scheme 1).[9–18] The structures of the products were determined by ^{1}H NMR, IR and elemental analysis and in most

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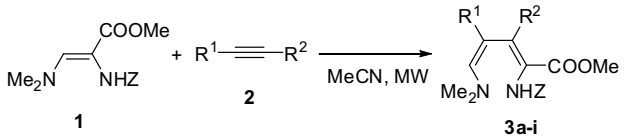


Comp.	Z	R^1	R^2	Yield (%)	Time (min)
3a	COPh	COO-*t*-Bu	COO-*t*-Bu	62	200
3b	COMe	COOMe	COOMe	75	100
3c	COMe	COOEt	COOEt	62	120
3d	COMe	COO-*t*-Bu	COO-*t*-Bu	73	200
3e	Cbz	COOMe	COOMe	84	120
3f	Cbz	COOEt	COOEt	69	120
3g	COPh	COOEt	H	40	180
3h	COPh	COOEt	CF_3	92	120
3i	COMe	COOEt	CF_3	77	120

Scheme 1. Microwave-assisted [2+2] cycloadditions.

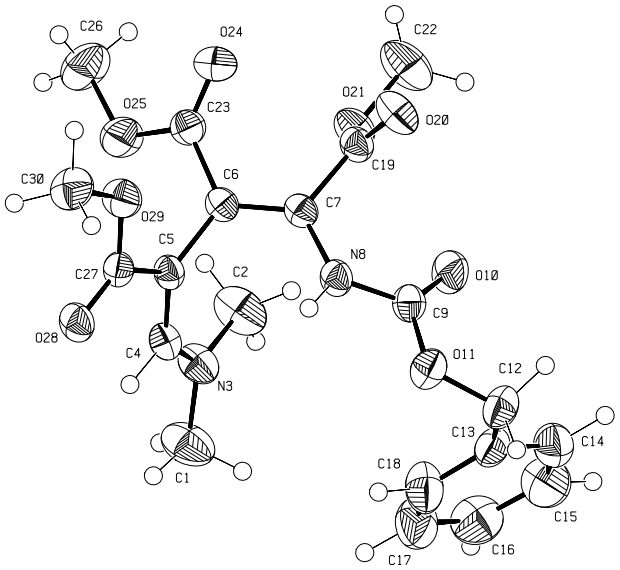
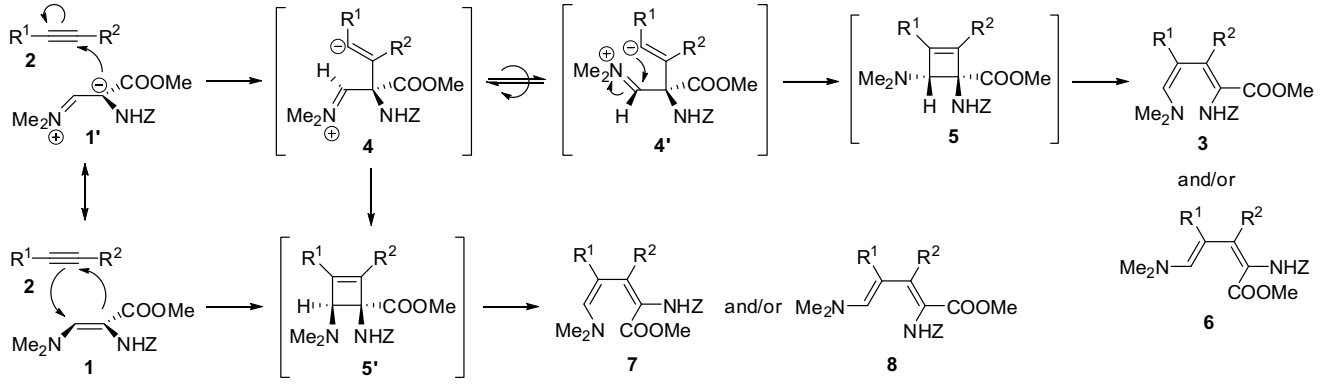


Fig. 1. ORTEP view of compound **3e**.

cases also by ^{13}C NMR, MS and HRMS. Additionally, the structures of **3e**,**h** were confirmed by X-ray diffraction.

For the cycloaddition reactions of acetylenes **2** to methyl (*Z*)-2-acylamino-3-(dimethylamino)propenoates **1** we envision two major pathways, a concerted and a stepwise one. In the case of a concerted cycloaddition the reaction should proceed as a [2_s+2_a] cycloaddition resulting in cyclobutene intermediate **5′**, which would undergo a conrotatory retro-electrocyclisation to afford (1*Z*,3*E*)-isomer **7** ($R^2 \neq H$) and/or (1*E*,3*Z*)-isomer **8** ($R^2 \neq H$) or (2*E*,4*E*)-isomer **7** ($R^2 = H$) and/or (2*Z*,4*Z*)-isomer **8** ($R^2 = H$). In the two-step mechanism, the initially formed intermediate **4** is transformed into **4′**, which gives sterically favoured cyclobutene intermediate **5**. This is then followed by a conrotatory retro-electrocyclisation to produce (1*E*,3*E*)-isomer **3** ($R^2 \neq H$) and/or (1*Z*,3*Z*)-isomer **6** ($R^2 \neq H$) or (2*Z*,4*E*)-isomer **3** ($R^2 = H$) and/or (2*E*,4*Z*)-isomer **6** ($R^2 = H$) (Scheme 2). Due to the fact that the C-2 carbon in methyl (*Z*)-2-acylamino-3-(dimethylamino)propenoates **1** possesses nucleophilic character,[3d] as shown by the resonance structure **1′**, it is apparent that these cycloadditions proceed preferentially by a stepwise mechanism.

The obtained X-ray structure of product **3e** (Fig. 1)[19] clearly demonstrates the orientation around the double bonds to be (1*E*,3*E*), indicating that these reactions most probably proceed by a two-step mechanism. In addition, in the case of a two-step mechanism one would expect that when a non-symmetrically substituted acetylene is used, only one regioisomer would be formed. This was in fact confirmed by performing reactions with ethyl propiolate and ethyl 4,4,4-trifluorobut-3-ynoate. In all cases only a single product was obtained. The structure of the regioisomer formed in the reaction with ethyl propiolate was determined by ^1H NMR. The absence of proton-proton couplings in the butadiene part indicates the formation of regioisomer **3g** and not **3g′** (Fig. 2). Analogously, the cycloaddition of ethyl 4,4,4-trifluorobut-3-ynoate was also regiospecific producing **3h** or **3i**; the structure of regioisomer **3h** was determined by X-ray analysis (Fig. 3).[20]



Scheme 2. Proposed mechanisms of the cycloadditions.

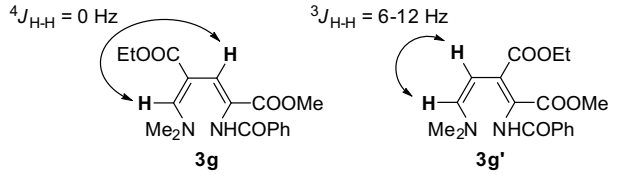


Fig. 2. Structure determination of the product obtained with ethyl propiolate.

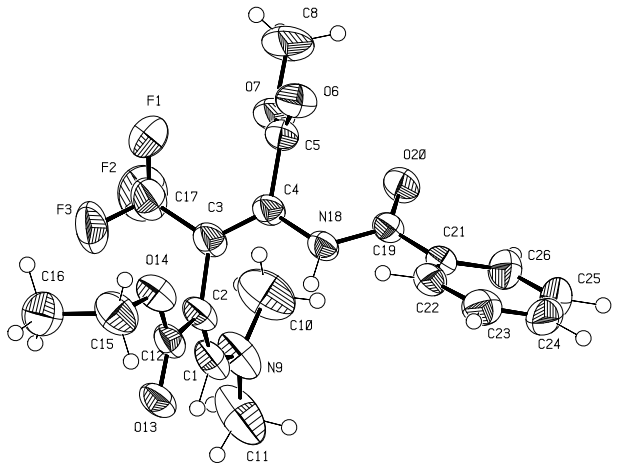


Fig. 3. ORTEP view of compound **3h**.

The X-ray structure of product **3h** additionally confirms the configurations around the double bonds to be the same as in the case of **3e**.

In this manner we have prepared a series of new highly functionalised buta-1,3-dienes, which in addition to up to three ester groups possess also a dimethylaminomethylidene moiety and as such offer wide possibilities for further transformations.

Acknowledgements

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9. *General procedure for the synthesis of 1-acylamino-4-(dimethylamino)buta-1,3-dienes* **3a**– **k**: Acetylene **2** (1.49–4 mmol) was added to a solution of 2-acylamino-3-(dimethylamino)propenoate **1** (1 mmol) in acetonitrile (4 mL) and the mixture was stirred in a closed vessel under microwave irradiation at automatically controlled constant temperature (CEM Corporation Discover microwave unit). The reaction mixture was cooled. Volatile components were evaporated in vacuo and the residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether 50–100% of ethyl acetate). Fractions containing the product were combined and evaporated in vacuo.
10. *2,3-Di-tert-butyl 1-methyl (1E,3E)-1-(benzoylamino)-4-(dimethylamino)buta-1,3-diene-1,2,3-tricarboxylate* (**3a**): Prepared from **1** (Z = COPh) (0.248 g, 1 mmol) and **2** ($R^1 = R^2$ = COO-*t*-Bu) (0.679 mL, 3 mmol), 80 °C, 200 min, chromatography (ethyl acetate/petroleum ether = 5:1), crystallisation (ethyl acetate/*n*-heptane = 1:1). Yield: 0.305 g (62%); mp 160–162 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (9H, s, C*Me*$_3$); 1.49 (9H, s, C*Me*$_3$); 2.84 (6H, s, N*Me*$_2$); 3.88 (3H, s, COO*Me*); 7.29 (1H, br s, N*H*); 7.43–7.49 (2H, m, 2H of *Ph*); 7.50 (1H, s, 4-*H*); 7.53–7.59 (1H, m, 1H of *Ph*); 7.70–7.75 (2H, m, 2H of *Ph*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 28.4, 28.8, 53.0, 80.3, 81.6, 91.6, 121.7, 127.5, 129.3, 132.1, 132.9, 133.0, 150.8, 164.8, 165.0, 166.2, 168.4. ($C_{25}H_{34}N_2O_7$ requires: C, 63.27; H, 7.22; N, 5.90. Found: C, 63.15; H, 7.37; N, 6.11); ν_{max} (KBr) 3296, 2974, 2945, 1746, 1737, 1724, 1684, 1650, 1602, 1435, 1366, 1293, 1272, 1255, 1168, 1146, 1088, 716 cm^{-1}.
11. *Trimethyl (1E,3E)-1-(acetylamino)-4-(dimethylamino)buta-1,3-diene-1,2,3-tricarboxylate* (**3b**): Prepared from **1** (Z = COMe) (0.186 g, 1 mmol) and **2** ($R^1 = R^2$ = COOMe) (0.250 mL, 2 mmol), 80 °C, 100 min, chromatography (ethyl acetate), crystallisation (ethyl acetate/petroleum ether). Yield: 0.246 g (75%); mp 160–163 °C. EI-MS: *m*/*z* = 328 (M^+). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.05 (3H, s, CO*Me*); 2.96 (6H, br s, N*Me*$_2$); 3.63 (3H, s, COO*Me*); 3.71 (3H, s, COO*Me*); 3.84 (3H, s, COO*Me*); 7.09 (1H, br s, N*H*); 7.56 (1H, s, 4-*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 23.0, 51.7, 52.7, 53.0, 89.5, 118.5, 134.0, 151.9, 165.1, 167.9, 168.7. ($C_{14}H_{20}N_2O_7$ requires: C, 51.22; H, 6.14;

N, 8.53. Found: C, 51.29; H, 6.24; N, 8.58); EI-HRMS: $m/z =$ 328.128005 (M^+); $C_{14}H_{20}N_2O_7$ requires: $m/z = 328.127051$ (M^+); ν_{max} (KBr) 3258, 2998, 2954, 1727, 1692, 1680, 1609, 1493, 1435, 1404, 1372, 1325, 1269, 1222, 1141, 1096, 1060, 1040, 894, 779, 764 cm^{-1}.

12. *2,3-Diethyl 1-methyl (1E,3E)-1-(acetylamino)-4-(dimethylamino)-buta-1,3-diene-1,2,3-tricarboxylate* (**3c**): Prepared from **1**(Z = COMe) (0.186 g, 1 mmol) and **2** ($R^1 = R^2 =$ COOEt) (0.325 mL, 2 mmol), 80 °C, 120 min, chromatography (ethyl acetate), crystallisation (ethyl acetate/petroleum ether = 1:1). Yield: 0.222 g (62%); mp 155–158 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (3H, t, $J = 7.1$ Hz, CH_2CH_3); 1.25 (3H, t, $J = 7.1$ Hz, CH_2CH_3); 2.04 (3H, s, CO*Me*); 2.96 (6H, br s, N*Me*$_2$); 3.83 (3H, s, COO*Me*); 3.96–4.22 (4H, m, 2 × CH_2CH_3); 6.98 (1H, br s, N*H*); 7.56 (1H, s, 4-*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.4, 14.6, 22.9, 52.9, 60.4, 61.4, 90.0, 119.5, 133.1, 151.9, 165.1, 167.5, 168.8, 169.4. ($C_{16}H_{24}N_2O_7$ requires: C, 53.92; H, 6.79; N, 7.86. Found: C, 54.14; H, 6.95; N, 8.11); ν_{max} (KBr): 3269, 2981, 1734, 1712, 1665, 1609, 1506, 1407, 1328, 1288, 1268, 1248, 1210, 1107, 1096, 1061, 987, 943, 777 cm^{-1}.
13. *2,3-Di-tert-butyl 1-methyl (1E,3E)-1-(acetylamino)-4-(dimethylamino)buta-1,3-diene-1,2,3-tricarboxylate* (**3d**): Prepared from **1** (Z = COMe) (0.186 g, 1 mmol) and **2** ($R^1 = R^2 =$ COO-*t*-Bu) (0.679 mL, 3 mmol), 80 °C, 200 min, chromatography (ethyl acetate/petroleum ether = 4:1), crystallisation (*n*-hexane). Yield: 0.300 g (73%); mp 73–77 °C. EI-MS: $m/z = 412$ (M^+). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.44 (9H, s, C*Me*$_3$); 1.46 (9H, s, C*Me*$_3$); 2.03 (3H, s, CO*Me*); 2.93 (6H, br s, N*Me*$_2$); 3.82 (3H, s, COO*Me*); 6.65 (1H, br s, N*H*); 7.49 (1H, s, 4-*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 23.3, 28.3, 28.7, 52.9, 80.2, 81.5, 91.4, 121.3, 131.9, 151.1, 165.1, 166.3, 168.0, 168.6. ($C_{20}H_{32}N_2O_7$ requires: C, 58.24; H, 7.82; N, 6.79. Found: C, 58.25; H, 8.04; N, 6.75); EI-HRMS: $m/z = 412.221850$ (M^+); $C_{20}H_{32}N_2O_7$ requires: $m/z = 412.220952$ (M^+); ν_{max} (KBr) 3274, 2978, 2931, 1739, 1714, 1692, 1666, 1608, 1479, 1434, 1391, 1367, 1303, 1251, 1204, 1166, 1092, 999, 841, 768 cm^{-1}.
14. *Trimethyl (1E,3E)-1-[(benzyloxycarbonyl)amino]-4-(dimethylamino)-buta-1,3-diene-1,2,3-tricarboxylate* (**3e**): Prepared from **1** (Z = Cbz) (0.278 g, 1 mmol) and **2** ($R^1 = R^2 =$ COOMe) (0.338 mL, 2.5 mmol), 90 °C, 120 min, chromatography (ethyl acetate/petroleum ether = 1:1), crystallisation (ethyl acetate/petroleum ether = 1:1). Yield: 0.354 g (84%); mp 159–161 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.85 (6H, br s, N*Me*$_2$); 3.62 (3H, s, COO*Me*); 3.71 (3H, s COO*Me*); 3.85 (3H, br s, COO*Me*); 5.06 (1H, d, $J = 12.0$ Hz, H_a–CH–Ph); 5.21 (1H, d, $J = 12.0$ Hz, H_b–CH–Ph); 6.23 (1H, br s, N*H*); 7.33–7.38 (5H, m, *Ph*); 7.53 (1H, s, 4-*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 51.8, 52.7, 53.2, 68.4, 88.6, 115.0, 129.0, 129.0, 129.1, 135.3, 135.7, 151.6, 152.6, 164.7, 167.5, 169.2.($C_{20}H_{24}N_2O_8$ requires: C, 57.14; H, 5.75; N, 6.66. Found: C, 57.18; H, 5.87; N, 6.85); ν_{max} (KBr) 3210, 2954, 1747, 1737, 1712, 1682, 1615, 1594, 1503, 1437, 1343, 1290, 1261, 1219, 1191, 1144, 1098, 1079, 1036, 1001, 766, 736, 696 cm^{-1}.
15. *2,3-Diethyl 1-methyl (1E,3E)-1-[(benzyloxycarbonyl)amino]-4-(dimethylamino)buta-1,3-diene-1,2,3-tricarboxylate* (**3f**): Prepared from **1** (Z = Cbz) (0.278 g, 1 mmol) and **2** ($R^1 = R^2 =$ COOEt) (0.400 mL, 2.5 mmol), 90 °C, 120 min, chromatography (ethyl acetate/petroleum ether = 1:1), crystallisation (ethyl acetate/petroleum ether = 1:1). Yield: 0.311 g (69%); mp 78–80 °C. EI-MS: $m/z = 448$ (M^+). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, t, $J = 7.1$ Hz, CH_2CH_3); 1.24 (3H, t, $J = 7.1$ Hz, CH_2CH_3); 2.83 (6H, br s, N*Me*$_2$); 3.83 (3H, br s, COO*Me*); 3.98–4.20 (4H, m, 2 × CH_2CH_3); 5.05 (1H, d, $J = 12.0$ Hz, H_a–CH–Ph); 5.22 (1H, d, $J = 12.0$ Hz, H_b–CH–Ph); 6.22 (1H, br s, N*H*); 7.33–7.38 (5H, m, *Ph*); 7.52 (1H, s, 4-*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.5, 14.8, 53.1, 60.3, 61.4, 68.3, 89.3, 115.3, 129.0, 129.0, 129.1, 134.2, 135.8, 151.5, 152.7, 164.7, 167.1, 168.8. ($C_{22}H_{28}N_2O_8$ requires: C, 58.92; H, 6.26; N, 6.25. Found: C, 58.87; H, 6.17; N, 6.48); EI-HRMS: $m/z = 448.185600$ (M^+); $C_{22}H_{28}N_2O_8$ requires: $m/z = 448.184566$ (M^+); ν_{max} (KBr) 3195, 2982, 1737, 1724, 1714, 1678, 1594, 1504, 1434, 1366, 1328, 1288, 1223, 1093, 1037, 989, 772, 759, 702 cm^{-1}.
16. *5-Ethyl 1-methyl (2Z,4E)-2-(acetylamino)-4-[(dimethylamino)methylene]pent-2-enedioate* (**3g**): Prepared from **1** (Z = COPh) (0.248 g, 1 mmol) and **2** ($R^1 =$ COOEt, $R^2 =$ H) (0.410 mL, 4 mmol), 100 °C, 180 min, chromatography (ethyl acetate). Yield: 0.137 g (40%); mp 128–132 °C. EI-MS: $m/z = 346$ (M^+). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (3H, t, $J = 7.1$ Hz, CH_2CH_3); 3.13 (6H, s, N*Me*$_2$); 3.80 (3H, 3, COO*Me*); 4.18 (2H, q, $J = 7.1$ Hz, CH_2CH_3); 7.06 (1H, s, 3-*H*); 7.40–7.54 (3H, m, 3H of *Ph*); 7.58 (1H, s, 1′-*H*); 7.87–7.92 (2H, m, 2H of *Ph*); 8.91 (1H, br s, N*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.9, 44.5, 52.6, 60.6, 92.8, 123.8, 125.3, 127.8, 128.9, 132.0, 134.2, 154.7, 165.1, 166.3. ($C_{18}H_{22}N_2O_5$ requires: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.45; H, 6.45; N, 8.02); EI-HRMS: $m/z = 346.153040$ (M^+); $C_{18}H_{22}N_2O_5$ requires: $m/z = 346.152872$ (M^+); ν_{max} (KBr) 3270, 2977, 2951, 1719, 1660, 1597, 1507, 1470, 1434, 1403, 1368, 1300, 1281, 1242, 1214, 1152, 1112, 1083, 757, 708 cm^{-1}.
17. *5-Ethyl 1-methyl(2E,4E)-2-(benzoylamino)-4-[(dimethylamino)methylene]-3-(trifluoromethyl)pent-2-enedioate* (**3h**): Prepared from **1** (Z = COPh) (0.248 g, 1 mmol) and **2** ($R^1 =$ COOEt, $R^2 = CF_3$) (0.262 mL, 1.58 mmol), 80 °C, 120 min, chromatography (ethyl acetate/petroleum ether = 1:1), crystallisation (ethyl acetate/petroleum ether = 1:1). Yield: 0.382 g (92%); mp 129–130 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (3H, t, $J = 7.1$ Hz, CH_2CH_3); 3.00 (6H, br s, N*Me*$_2$); 3.94 (3H, s, COO*Me*); 4.05–4.16 (1H, m, H_a–CH–CH_3); 4.20–4.30 (1H, m, H_b–CH–CH_3); 7.44–7.51 (2H, m, 2H of *Ph*); 7.55–7.62 (1H, m, 1H of *Ph*); 7.66 (1H, br s, N*H*); 7.67 (1H, s, 1′-*H*); 7.70–7.74 (2H, m, 2H of *Ph*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.2, 52.9, 60.2, 84.3 (q, $J = 1.6$ Hz), 112.5 (q, $J = 33.6$ Hz), 122.8 (q, $J = 273$ Hz), 127.2, 128.9, 132.0, 132.8, 134.4 (q, $J = 3.1$ Hz), 151.8, 163.3, 164.2, 168.2. ($C_{19}H_{21}F_3N_2O_5$ requires: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.45; H, 6.45; N, 8.02); ν_{max} (KBr) 3220, 2952, 1746, 1691, 1673, 1637, 1592, 1503, 1483, 1436, 1367, 1327, 1295, 1266, 1223, 1153, 1112, 1083, 979, 761 cm^{-1}.
18. *5-Ethyl 1-methyl (2E,4E)-2-(acetylamino)-4-[(dimethylamino)methylene]-3-(trifluoromethyl)pent-2-enedioate* (**3i**): Prepared from **1** (Z = COMe) (0.186 g, 1 mmol) and **2** ($R^1 =$ COOEt, $R^2 = CF_3$) (0.248 mL, 1.49 mmol), 80 °C, 120 min, chromatography (ethyl acetate), crystallisation (ethyl acetate/petroleum ether = 1:1). Yield: 0.271 g (77%); mp 167–170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (3H, t, $J = 7.1$ Hz, CH_2CH_3); 2.07 (3H, s, CO*Me*); 3.01 (6H, br s, N*Me*$_2$); 3.87 (3H, s, COO*Me*); 4.00–4.12 (1H, m, H_a–CH–CH_3); 4.16–4.28 (1H, m, H_b–CH–CH_3); 7.05 (1H, br s, N*H*); 7.62 (1H, s, 1′-*H*). ($C_{14}H_{19}F_3N_2O_5$ requires: C, 47.73; H, 5.44; N, 7.95. Found: C, 47.71; H, 5.60; N, 7.80); ν_{max} (KBr) 3252, 2983, 2955, 1746, 1706, 1686, 1638, 1594, 1503, 1434, 1332, 1297, 1271, 1236, 1147, 1114, 1092, 1019, 765 cm^{-1}.
19. Crystallographic data (excluding structure factors) for structure **3g** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 679308. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
20. Crystallographic data (excluding structure factors) for structure **3j** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 679309. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].