Reaction between alkyl or aryl isocyanides and dialkyl acetylenedicarboxylates in the presence of *N,N′*-dimethylbarbituric acid: synthesis of 4*H*-pyrano[2,3-*d*]pyrimidines

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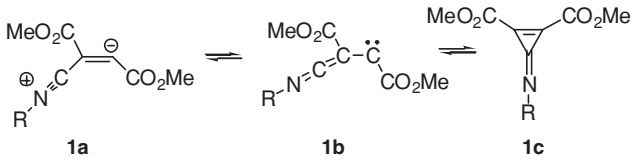
The highly reactive 1:1 adduct produced in the reaction between alkyl or aryl isocyanides and dialkyl acetylenedicarboxylates is trapped by *N,N′*-dimethylbarbituric acid to yield 4*H*-pyrano[2,3-*d*]pyrimidine derivatives.

Keywords: isocyanides, acetylenicester, *N,N′*-dimethylbarbituric acid, 4*H*-pyranopyrimidine, enaminoester

The addition of isocyanides to dimethyl acetylenedicarboxylates (DMAD) has been investigated in detail.[1-3] The initially formed 1:1 zwitterionic species (**1a–c**) (Scheme 1) undergo further reactions with DMAD and isocyanide in different molar proportions, ultimately leading to a variety of complex heterocyclic systems.[4-8] This highly activated zwitterion can manifest carbanion or carbene character or even resemble a cyclopropenone imine. We recently reported the reaction between isocyanides and dimethyl acetylenedicarboxylate (DMAD) in the presence of *N,N′*-dimethylbarbituric acid.[9]

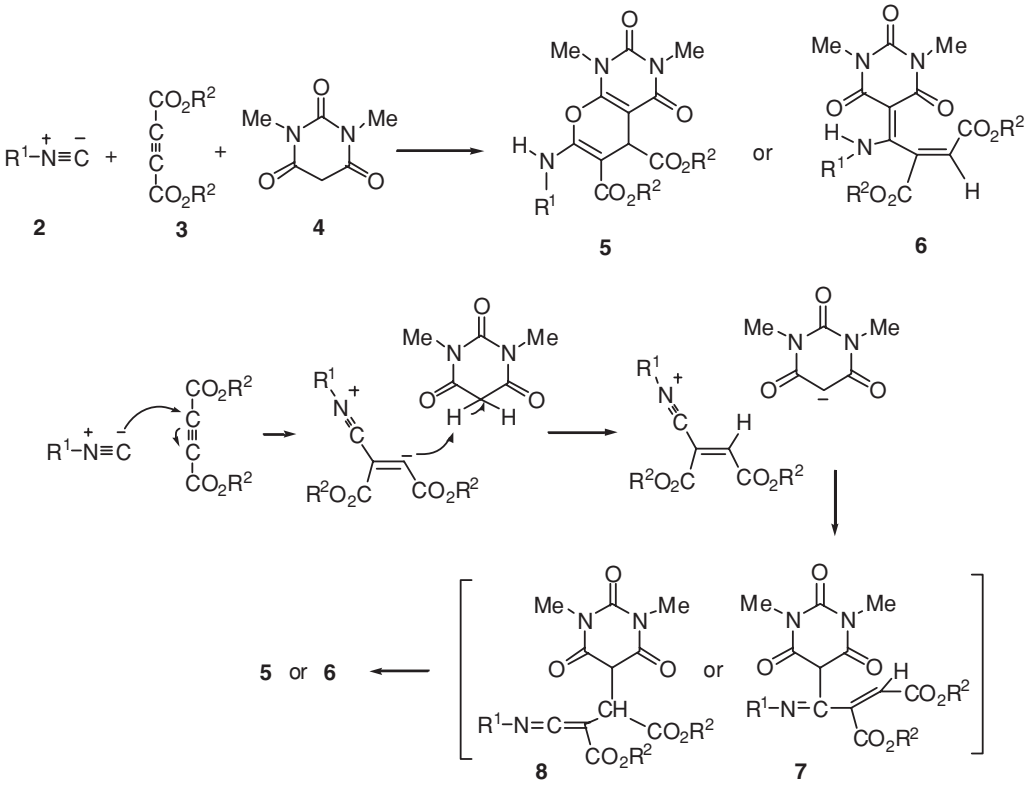
We extend these reaction to various dialkyl acetylenedicarboxylates and alkyl or aryl isocyanides and we present our results herein.

The reaction of alkyl or aryl isocyandes and dialkyl acetylenedicarboxylates in the presence of *N,N′*-dimethylbarbituric acid undergo a smooth reaction in dichloromethane at room temperature to produce the isomeric products (**5**) and (**6**) (see Scheme 2).



Scheme 1

On the basis of the well established chemistry of isocyanides[1-4] it is reasonable to assume that compounds (**5**) and (**6**) result from initial addition of the alkyl isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct by *N,N′*-dimethylbarbituric acid (Table 1). Then the positively charged ion might be attacked by the enolate anion of the CH acid in two ways. The first, which is a Michael addition, leads to the ketenimine (**8**). Such an addition product may isomerize under the reaction condition employed to produce the fused heterocyclic system (**5**). The second, which involves



Scheme 2

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Table 1 Addition process

Products	R^1	R^2	Yield/%
5a	*t*-Bu	Et	78
5b	*t*-Bu	*t*-Bu	90
5c	Cyclohexyl	Et	78
5d	Cyclohexyl	*t*-Bu	85
5e	2, 6-Me_2-C_6H_3	Et	90
5f	2, 6-Me_2-C_6H_3	*t*-Bu	85
6a	Bn	Me	90
6b	Bn	Et	85
6c	Bn	*t*-Bu	78

direct addition of enolate anion to the positive ion, produce heterodiene (**6**). This addition product undergoes an imine-to-enamine tautomerism to generate the enaminone system (**6**). The (**E**) configuration of the carbon–carbon double bond in (**6**) is based on the chemical shift of the olefinic proton.

Structure (**5**) was assigned to the isolated products on the basis of their IR, ^{1}H, ^{13}C NMR and mass spectral data. The mass spectra of 4*H*-pyrano[2,3-*d*]pyrimidines (**5a–f**) are similar, as expected, and the confirm their molecular weights. Initial fragmentations involve loss of the side chains and scission of the enaminoester system.

The ^{1}H NMR spectrum of compound (**5a**) exhibited nine single sharp lines, readily recognisable as arising from *C*-methyl (δ = 1.22 and 1.25), *tert*-butyl (δ = 1.41), *N*-methyl (δ = 3.28 and 3.51), methylene (δ = 4.07 and 4.21), methine (δ = 4.53) and NH group exhibits a broad band at δ = 8.95 ppm, indicating intramolecular hydrogen bond formation with the vicinal carbonyl group.

The ^{13}C NMR spectrum showed seventeen distinct resonance consistent with enaminoester structure.

The structural assignments of compounds (**5a–f**) made on the basis of their NMR spectra were supported by their IR spectra. of special interest are the strong carbonyl absorption bands at 1552–1717 cm^{-1} for all compounds and fairly broad NH peak at about 3250–3400 cm^{-1} (see experimental section).

Structure (**6**) was assigned to the isolated products on the basis of their IR, ^{1}H, ^{13}C NMR and mass spectral data. IR spectroscopy was used to distinguish compound (**6**) from the primary product, the ketenimine derivative (**6**). The mass spectra of enaminoesters (**6a–c**) are similar, as expected, and the confirm their molecular weights. Initial fragmentations involve loss of the side chains and scission of the enaminoester system.

The ^{1}H NMR spectrum of compound (**6a**) exhibited eight single sharp lines, readily recognisable as arising from *N*-methyl (δ = 3.20 and 3.31), methoxy (δ = 3.69 and 3.82), methylene (δ = 4.43), methine (δ = 7.00), Ar methine (δ=7.32), NH (δ=12.49) a long with fairly complex multiplet in the aromatic region. The ^{13}C NMR spectrum showed eighteen distinct resonance consistent with enaminoester structure.

The structural assignments of compounds (**6a–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 1580–1720 cm^{-1} for all compounds and fairly broad NH peak at about 3400 cm^{-1} (see experimental section).

In summary, the reaction of alkyl or aryl isocyanides with electron-deficient acetylenic esters in the presence of *N,N′*-dimethylbarbituric acid provides a simple one-pot entry into the synthesis of polyfunctional enaminoester and 4*H*-pyrano[2,3-*d*]pyrimidine of potential synthetic interest.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental anal analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyser. IR spectra were measured on a Shimadzu IR-460 spectrometer, ^{1}H and ^{13}C NMR spectra with a Bruker-500 and 125.7 MHz spectrometer, respectively, and mass spectra on a Shimadzu QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Isocyanides, alkyl acetylenedicarboxylates, *N,N′*-dimethylbarbituric acid were obtained from Fluka (Buchs, Switzerland) and used without further purification.

The process for the preparation of *Diethyl 7-tert-Butylamino-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate* (**5a**): is described as an example. To magnetically stirred solution of N,N´-dimethylbarbituric acid (0.156 g, 1mmol) and diethyl acetylenedicarboxylate (0.17 g,1mmol) in CH_2Cl_2 (6 ml) was added, dropwise, a mixture of *tert*-butyl isocyanide(0.831 g,1mmol) in CH_2Cl_2 (2 ml) was added dropwise at –10 °C over 10 min the reaction mixture was then allowed to warm up to room temperature and to stand for 5 days. The solvent was removed under reduced pressure and the solid residue was washed by (2 × 3) cm^3 cold diethyl ether and the product **5a** was obtained as pale yellow powder, m.p. 116–118 °C, yield: 0.32 g (78%), IR (KBr) (ν_{max}, cm^{-1}): 3270 (N–H); 1606, 1652, 1716 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.22 and 1.25 (6 H, t, 2 Me of 2 CH_2CH_3), 1.41 (9 H, s, CMe_3), 3.28 and 3.51 (6 H, s, 2 N–CH_3), 4.07 and 4.21 (4 H, m, 2 OCH_2), 4.53 (1 H, s, CH), 8.95 (1H, br s, NH...O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 14.03 and 14.07 (2 CH_2CH_3), 30.28 (3 Me of CMe_3), 28.16 and 30.20 (2 N–CH_3), 35.54 (CH), 52.60 (CMe_3), 59.93 and 61.05 (2 OCH_2), 74.05 and 88.44 (2 *C*=C–O), 150.23 and 151.53 (2 C=C–O), 158.83 (NCON), 161.11 (NCO), 168.93 and 173.67 (2 C=O). MS (*m/z*, %): 411 (M$^+$+2, 5), 410 (M$^+$+1, 20), 409 (M$^+$, 5), 336 (100), 280 (85), 234 (75), 222 (4), 57 (68). Anal Calcd for $C_{19}H_{27}N_3O_7$ (409.44): C, 55.74; H, 6.60; N, 10.27%; Found: C, 55.73; H, 6.61; N, 10.25%.

Di-tert-butyl 7-tert-butylamino-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]-pyrimidine-5,6-dicarboxylate (**5b**): Pale yellow powder, m.p. 146–148 °C, yield: 0.42 g (90%), IR (KBr) (ν_{max}, cm^{-1}): 3400 (N-H); 1652, 1683, 1712 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.42 (9 H, s, $NCMe_3$), 1.43 and 1.49 (18 H, s, 2 CMe_3), 3.34, 3.51 (6 H, s, 2 NCH_3), 4.42 (1 H, s, CH), 8.91 (1 H, s, NH...O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 28.06 (3Me of $NCMe_3$), 28.29 and 28.48 (2 N–CH_3), 30.30 and 30.54 (6 Me of 2 CMe_3), 36.92 (CH), 51.65 (N–CMe_3), 80.29 and 81.10 (2 *C*Me_3), 75.81 and 89.23 (2 *C*=C–O), 150.49 and 151.73 (2 C=*C*–O), 158.81 (NCON), 166.85 (NCO), 169.81, 173.40 (2 C=O). MS (*m/z*, %): 466 (M$^+$+1, 5), 364 (10), 308 (15), 209 (20), 159 (20), 57 (100). Anal Calcd for $C_{23}H_{35}N_3O_7$ (465.44): C, 59.35; H, 7.53; N, 9.03%; Found: C, 59.28; H, 7.55; N, 9.10%.

Diethyl 7-cyclohexylamino-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**5c**): Pale yellow powder, m.p. 128–130 °C, yield: 0.34 g (78%), IR (KBr) (ν_{max}, cm^{-1}): 3350 (N–H); 1651, 1709 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.32–2.10 (10 H, m, 5 CH_2), 1.25, 1.36 (6 H, t, 2 Me of 2 CH_2CH_3), 3.34, 3.46 (6 H, s, 2 N–CH_3), 3.62 (1 H, s, NCH), 4.12 and 4.21 (4 H, m, 2 OCH_2), 4.58 (1 H, s, CH), 8.72 (1H, s, NH...O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 14.18 and 14.43 (2 CH_2CH_3), 24.43, 24.58 and 25.38 (3 CH_2 of Cyclohexyl), 28.34 and 29.05 (2 N–CH_3), 33.41 and 33.76 (2 CH_2 of Cyclohexyl), 35.75 (CH), 50.90 (N–CH), 59.96 and 61.26 (2 OCH_2), 73.18 and 88.62 (2 *C*=C–O), 150.41 and 151.53 (2 C=*C*–O), 157.74 (NCON), 161.24 (NCO), 168.90, 173.90 (2 C=O). MS (*m/z*, %): 436 (M$^+$+1, 2), 308 (15), 281 (45), 235 (100), 98 (90), 83 (25). Anal Calcd for $C_{21}H_{29}N_3O_7$ (435.48): C, 57.93; H, 6.67; N, 9.66%; Found: C, 57.91; H, 6.69; N, 9.64%.

Di-tert-butyl 7-cyclohexylamino-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]-pyrimidine-5,6-dicarboxylate (**5d**): Pale yellow powder, m.p. 161–163 °C, yield: 0.42 g (85%), IR (KBr) (ν_{max}, cm^{-1}): 3380 (N–H); 1655, 1690, 1717 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.34–2.10 (10 H, m, 5 CH_2), 1.44 and 1.49 (18 H, s, 2 CMe_3), 3.32 and 3.43 (6 H, s, 2 N–CH_3), 3.45 (1 H, m, N–CH), 4.42 (1 H, s, CH), 8.65 (1 H, s, NH...O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 27.94 and 28.4 (6 Me of 2 C*Me*$_3$), 24.48, 24.54 and 25.26, (3 CH_2 of Cyclohexyl), 28.09 and 28.86 (2 N–CH_3), 33.44 and 33.81 (2 CH_2 of Cyclohexyl), 50.85 (N–CH), 36.88 (CH), 79.94 and 80.91 (2 *C*Me_3), 74.69 and 89.03 (2 *C*=C–O), 150.32 and 151.56 (2 C=*C*–O), 157.55 (NCON), 161.01 (NCO), 168.33 and 173.28 (2 C=O). MS (*m/z*, %): 493 (M$^+$+2, 5), 492 (M$^+$+1, 10), 491 (M$^+$, 3), 390 (30), 334 (100), 57 (95). Anal Calcd for $C_{25}H_{37}N_3O_7$ (491.59): C, 61.10; H, 7.53; N, 8.55%; Found: C, 61.12; H, 7.51; N, 8.57%.

Diethyl 7-(2,6-dimethylphenylamino)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (**5e**): Pale yellow powder, m.p. 135–137 °C, yield: 0.41 g (90%), IR (KBr) (ν_{max}, cm^{-1}): 3270 (N–H); 1660, 1695, 1715, 1725, (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.29 and 1.33 (6 H, t, 2 Me of 2 CH_2CH_3), 2.20 and 2.33 (6 H, s, 2 Me of $ArCH_3$), 2.79 and 3.29 (6 H, s, 2 N–CH_3), 4.18 and 4.27 (4 H, m, 2 OCH_2), 4.65 (1 H, s, CH), 7.09–7.13 (3 H,

m, ArH), 9.74 (1 H, S, NH...O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 14.19 and 14.39 (2 CH_2CH_3), 18.22 and 18.41 (Ar*Me*$_2$), 28.24 and 28.32 (2 N–CH_3), 35.91 (CH), 60.34 and 61.33 (2 OCH_2), 75.19 and 88.31 (2 *C*=C–O), 127.84, 128.13, 128.36, 133.81, 135.78 and 136.69 (6 C_{arom}), 150.22 and 151.53 (2 C=*C*–O), 157.23 (NCON), 161.15 (NCO), 168.81 and 173.37 (2 C=O). Anal Calcd for $C_{23}H_{27}N_3O_7$ (457.49): C, 60.39; H, 5.91; N, 9.19%; Found: C, 60.40; H, 5.92; N, 9.17%.

Di-tert-butyl 7-(2,6-dimethylphenylamino)-1,3-dimethyl-2, 4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5, 6-dicarboxylate (**5f**): Pale yellow powder, m.p. 142–144 °C, yield: 0.47 g (85%), IR (KBr) (ν_{max}, cm^{-1}): 3250 (N–H); 1650, 1660, 1690 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.47 and 1.56 (18 H, s, 2 CMe_3), 2.18 and 2.33 (6H, s, 2 Me of ArCH_3), 2.77 and 3.32 (6 H, s, 2 NCH_3), 4.51 (1 H, s, CH), 7.06–7.27 (3 H, m, ArH), 9.71 (1H, s, NH...O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 18.18, 18.50 (Ar*Me*$_2$), 27.89 and 28.27 (6 Me of 2 C*Me*$_3$), 28.50 and 29.72 (2 N–CH_3), 37.15 (CH), 81.17 and 88.99 (2 C=C–O), 127.61, 128.06, 128.27, 134.21, 135.79 and 136.83 (6 C_{arom}), 150.38 and 151.61 (2 C=*C*–O), 157.04 (NCON), 161.12 (NCO), 168.49, 172.52 (2 C=O). MS (*m/z*, %): 513 (M^+, 17), 412 (95), 392 (24), 356 (100), 312 (95), 236 (58), 179 (35), 57(40). Anal Calcd for $C_{27}H_{35}N_3O_7$ (513.60): C, 63.16; H, 6.82; N, 8.19%; Found: C, 63.09; H, 6.85; N, 8.17%.

The process for the preparation of *dimethyl (E)-2-[(benzylamino) (1,3-dimethyl-2,4,6-trioxo hexahydro pyrimidine-5-ylidene) methyl] butenedioate* (**6a**) is described as an example. To magnetically stirred solution of *N,N'*-dimethylbarbituric acid (0.156 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in CH_2Cl_2 (6 ml) was added, dropwise, a mixture of benzyl isocyanide (0.12 g, 1mmol) in CH_2Cl_2 (2 ml) was added dropwise at –10 °C over 10 min. The reaction mixture was then allowed to warm up to room temperature and to stand 5 days. The solvent was removed under reduced pressure and the solid residue was washed by (2×3) cm^3 cold diethyl ether and the product **6a** was obtained as Pale yellow powder, m.p. 128–130 °C, yield: 0.37 g (90%), IR (KBr) (ν_{max}, cm^{-1}): 3450 (N–H); 1580, 1630, 1720 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.20 and 3.31 (6 H, s, 2 N–CH_3), 3.69 and 3.82 (6 H, s, 2 O–CH_3), 4.43 (2 H, m, CH_2), 7.00 (1 H, s, CH), 7.32 (5 H, m, ArH), 12.49 (1 H, br s, N–H…O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 27.53 and 27.85 (2 N–CH_3), 49.00 (CH_2), 52.47 and 53.31 (2 OCH_3), 90.78 (*C*=C–N), 126.52, 127.91, 128.40 and 129.06 (6 C_{arom}), 134.98 and 140.02 (2 C_{sp2} RCO_2–*C*=*C*–CO_2R), 151.47 (C=*C*–N), 162.41, 162.74 and 164.22 (3 N–C=O), 165.68 and 166.61 (C=O). MS (*m/z*, %): 415 (M^+, 2), 400 (57), 340 (98), 280 (17), 106 (8), 91 (100), 58 (19). Anal Calcd for $C_{20}H_{21}N_3O_7$ (415.41): C, 57.83; H, 5.06; N, 10.12%; Found: C, 57.85; H, 5.10; N, 10.14%.

Diethyl (E)-2-[(benzylamino) (1,3-dimethyl-2,4,6-trioxo hexahydro pyrimidine-5-ylidene)methyl] butenedioate (**6b**): White powder, m.p. 135–137 °C, yield: 0.38 g (85%), IR (KBr) (ν_{max}, cm^{-1}): 3400 (N–H); 1680, 1720, 1738 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.24 and 1.28 (6 H, t, 2 CH_3), 3.23 and 3.32 (6 H, s, 2 N–CH_3), 4.06 and 4.28 (4 H, m, 2 OCH_2) , 4.46 (2 H, m, CH_2), 5.29 (1 H, s, CH), 7.27 (5 H, m, ArH), 12.47 (1 H, br s, N–H…O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 14.05 and 14.13 (2 CH_2CH_3), 27.63 and 27.93 (2 N–CH_3), 49.15 (CH_2), 61.69 and 62.60 (2 OCH_2), 90.89 (*C*=C–N), 126.99, 128.03, 128.52 and 129.17 (CAr), 135.15 and 140.19 (2 C_{sp2} RCO_2–*C*=*C*–CO_2R), 151.60 (C=*C*–N), 162.38, 162.46 and 163.92 (3 N–C=O), 165.82 and 167.01(C=O). MS (*m/z*, %): 443 (M^+, 38), 370 (95), 323 (98), 296 (83), 239 (16), 182 (17), 106 (15), 91 (100). Anal Calcd for $C_{22}H_{25}N_3O_7$ (443.46): C, 59.59; H, 5.64; N, 9.48%; Found: C, 59.62; H, 5.65; N, 9.51%.

Di-tert-butyl (E)-2-[(benzylamino) (1,3-dimethyl-2,4,6-trioxo-hexahydro pyrimidine-5-ylidene)methyl]butenedioat (**6c**): Yellow powder, m.p. 136–138 °C, yield: 0.39 g (78%), IR (KBr) (ν_{max}, cm^{-1}): 3450 (N–H); 1610, 1620 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.41 and 1.46 (18 H, s, CMe_3), 3.25 and 3.32 (6 H, s, 2 N–CH_3), 4.43 (2 H, m, CH_2), 5.29 (1 H, s, CH), 7.33 (5 H, m, ArH), 12.44 (1 H, br s, N–H…O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 27.49 and 27.77 (2 N–CH_3), 27.85 (6 Me of C*Me*$_3$), 48.95 (CH_2), 82.51 and 83.47 (2 *C*Me$_3$), 90.70 (*C*=C–N), 127.92, 128.35, 128.43 and 129.09 (C_{arom}), 135.05 and 139.96 (2 Csp^2 RCO_2–*C*=*C*–CO_2R), 151.65 (C=*C*–N), 161.39, 162.13 and 163.18 (3 N–C=O), 165.76 and 167.71 (C=O). MS (*m/z*, %): 501 (M^++2, 18), 500 (M^++1, 57), 499 (M^+, 46), 443 (20), 398 (95), 342 (98), 297 (97), 91 (100), 57 (73). Anal Calcd for $C_{26}H_{33}N_3O_7$ (499.57): C, 62.52; H, 6.61; N, 8.42%; Found: C, 62.48; H, 6.60; N, 8.44%.

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