SHORT PAPER

J. Chem. Research (S),
2002, 433–435

The reaction of alkyl isocyanides and benzylidene Meldrum's acid derivatives in the presence of water: a one-pot synthesis of 4-(alkylamino)-3-aryl-4-oxobutanoic acids†

Ahmad Shaabani[a,b]* and Mohammad Bagher Teimouri[a]

[a]*Department of Chemistry, Shahid Beheshti University, PO Box 19396-4716, Tehran, Iran*

[b]*Medicinal and Aromatic Plants and Drug Research Institute, Shahid Beheshti University, PO Box 19396-4716, Tehran, Iran*

The reaction between alkyl isocyanides and substituted-benzylidene Meldrum's acid derivatives in the presence of water produces 4-(alkylamino)-3-aryl-4-oxobutanoic acids in good yields.

Keywords: isocyanides, benzylidene Meldrum's acid, 4-(alkylamino)-3-aryl-4-oxobutanoic acid, arylsuccinic acid monoamides

Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione[1], and its benzylidene derivatives as dienophiles have been an important topic owing to their potential synthetic utility. We have recently reported a synthetic route for preparation of highly functionalised amidodiesters.[2] This reaction involved the [1+4] cycloaddition reaction of an alkyl isocyanide with the 4-nitrophenylmethylidene derivative of Meldrum's acid in the presence of alcohols.

In the present paper we report the reaction of alkyl isocyanides **1** and substituted-benzylidene Meldrum's acid derivatives **2** in the presence of water **3** in a one-pot synthesis of 4-(alkylamino)-3-aryl-4-oxobutanoic acid derivatives **4**, derivatives of which have potent antirheumatic effects and are suitable for clinical use.[3–5] This reaction proceeded spontaneously at room temperature in CH_2Cl_2 (for preparation of **4a** and **4b**) or CH_3CN (for preparation of **4c** and **4d**) (Scheme 1).

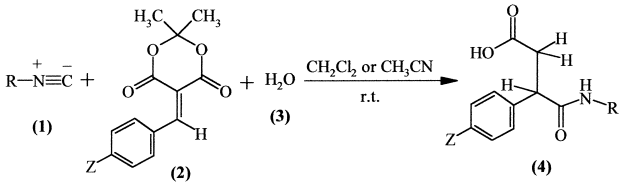
All the compounds **4a–d** are stable solids whose structures are fully supported by elemental analysis, ^1H and ^{13}C NMR and IR spectral data. The mass spectra of **4a–d** displayed M+1 peaks instead of molecular ion peaks at *m*/*z* 295, 321, 278 and 304 respectively.

The methylene group of compounds **4a–d** is attached to an asymmetric carbon atom bearing a hydrogen atom and the protons are therefore diastereotopic. Thus, the ^1H NMR spectrum of **4a** exhibited a single sharp line arising from the *tert*-butyl group (δ 1.16) along with a three-spin AMX system for methylene and methine protons. This leads to a doublet of doublets for each of the protons H^A, H^M and H^X at 2.53 (1H, dd, $^2J_{HH}$ = 16.6 Hz, $^3J_{HH}$ = 5.8 Hz, CH^AH), 2.90 (1H, dd, $^2J_{HH}$ = 16.6 Hz, $^3J_{HH}$ = 9.2 Hz, CHH^M) and 4.04 (1H, dd, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 5.8 Hz, CH^X), respectively. The 4-nitrophenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum and the NH proton resonated at δ 7.78, supporting the IR absorption at 3305 cm^{-1}. A fairly broad singlet was seen for the CO_2H group at δ 12.19.

The ^1H-decoupled ^{13}C NMR spectrum of **4a** showed 10 distinct resonances in agreement with the suggested structure. Partial assignment of these resonances is given in the Experimental section.

The ^1H and ^{13}C NMR spectra of **4b–d** are similar to those of **4a** except for differences in the alkylamino and 4-substituted phenyl groups, which exhibit characteristic signals with appropriate chemical shifts (see Experimental section).

We have not established a mechanism for the formation of 4-(alkylamino)-3-aryl-4-oxobutanoic acids **4**. However, a possible explanation is shown in Scheme 2. On the basis of the well established chemistry of isocyanides,[6–12] it is reasonable to assume that iminolactone **5** as an intermediate results from [1+4] cycloaddition reaction of the alkyl isocyanide with the electron-deficient heterodiene moiety of the benzylidene Meldrum's acid derivatives. Then, iminolactone **5** can by two different pathways afford compound **6**, which after decarboxylation would yield the 4-(alkylamino)-3-aryl-4-oxobutanoic acids **4**.



(4)	R	Z	Yield (%)
a	*tert*-Bu	NO_2	88
b	Cyclohexyl	NO_2	86
c	*tert*-Bu	CHO	83
d	Cyclohexyl	CHO	87

Scheme 1

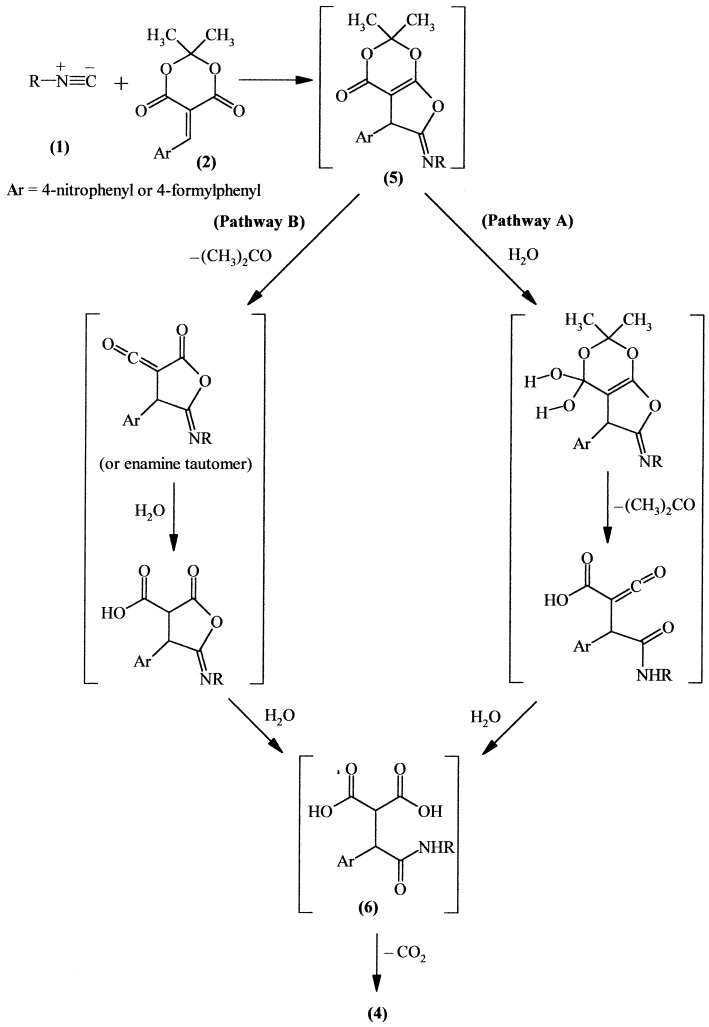
Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 Avance spectrometer at 500.13 and 125.77 MHz, respectively. NMR spectra were obtained on solutions in acetone-d_6 or DMSO-d_6. The chemicals used in this work were purchased from Fluka Chemical Company (Buchs, Switzerland). Isopropylidene *p*-nitrobenzalmalonate was prepared according to a published procedure.[13]

Preparation of isopropylidene 4-formylbenzalmalonate: A solution of isopropylidene malonate (1.44 g, 10 mmol) and terephthalaldehyde (0.67 g, 5 mmol) in dimethyl sulfoxide (10 ml) was allowed to stand at room temperature. After 8 h a white precipitate formed. Filtration and washing with diethyl ether gave the product (1.12 g, 43 %), m.p. 163–164°C. IR (KBr) (ν_{max}, cm^{-1}): 2745 (OC-H), 1765, 1727 and 1703 (C=O), 1604 (C=C). ^1H NMR (DMSO-d_6): δ_H 1.77 (6 H, s, $2CH_3$), 7.93 and 8.04 (4 H, 2d, $^3J_{HH}$ = 8.4 Hz, C_6H_4), 8.45 (1 H, s, C=CH), 10.06 (1 H, s, CHO). ^{13}C NMR (DMSO-d_6): δ_C 27.43 (2 CH_3), 105.48 (CMe_2), 129.44, 132.30, 132.68, 137.97, 138.26 and

* To receive any correspondence. E-mail: a-shaabani@cc.sbu.ac.ir

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



Scheme 2

155.41 (arom and C=C), 159.61 and 162.38 (2 C=O), 193.24 (CHO). MS (*m*/*z*, %) 260 (M^+, 5), 245 (19), 202 (15), 132 (12) 58 (20), 43 (100).

*Preparation of 4-(t-butylamino)-3-(4-nitrophenyl)-4-oxobutanoic acid (***4a***). Typical procedure*: To a magnetically stirred solution of isopropylidene *p*-nitrobenzalmalonate (0.280 g, 1 mmol) in water (5 ml) and dichloromethane (15 ml) was added dropwise a solution of *tert*-butyl isocyanide (0.084 g, 1 mmol) in dichloromethane (2 ml) at 0°C over 10 min. The reaction mixture was allowed to warm to room temperature (25°C) and stirred for 24 hours. The solution was concentrated to afford the white crystalline product. The product was filtered and washed with diethyl ether to yield **4a** as white crystals (0.259 g, 88 %), m.p. 208–209°C (dec.). IR (KBr) ($\nu_{max,}$ cm^{-1}): 3305 (N–H), 2600–3300 (O–H), 1708 and 1641 (C=O), 1512 and 1348 (NO_2). ^{1}H NMR (DMSO-d_6): δ_H 1.16 (9 H, s, CMe_3), 2.53 (1 H, dd, $^2J_{HH}$=16.6 Hz, $^3J_{HH}$=5.8 Hz, CH*H*), 2.90 (1 H, dd, $^2J_{HH}$=16.6 Hz, $^3J_{HH}$=9.2 Hz, C*H*H), 4.04 (1 H, dd, $^3J_{HH}$=9.2 Hz, $^3J_{HH}$=5.8 Hz, CH), 7.56 and 8.16 (4 H, $^3J_{HH}$=8.5 Hz, $C_6H_4NO_2$), 7.78 (1 H, s, NH), 12.19 (1 H, br s, CO_2H). ^{13}C NMR (DMSO-d_6): δ_C 28.79 (C*Me*$_3$), 37.65 (CH_2), 47.65 (*C*Me$_3$), 50.61 (CH), 123.87, 129.25, 146.85 and 148.77 (arom.), 170.60 and 172.82 (2 C=O). MS (*m*/*z*, %) 295 (MH^+, 97), 221 (14), 195 (100), 153 (98), 104 (17), 57 (97). Anal. Calcd. for $C_{14}H_{18}N_2O_5$ (294.33): C, 57.12; H, 6.16; N, 9.51%. Found: C, 56.93; H, 6.03; N, 9.42%.

In a similar way the products **4b–d** were obtained.

4-(Cyclohexylamino)-3-(4-nitrophenyl)-4-oxobutanoic acid (**4b**): White crystals (0.277 g, 86%), m.p. 214–215°C (dec.). IR (KBr) ($\nu_{max,}$ cm^{-1}): 3280 (N–H), 2600–3300 (O-H), 1708 and 1636 (C=O), 1512 and 1347 (NO_2). ^{1}H NMR (DMSO-d_6): δ_H 0.98–1.72 (10 H, m, 5 CH_2), 2.57 (1 H, dd, $^2J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 5.6 Hz, CH*H*), 2.94 (1 H, dd, $^2J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 9.1 Hz, C*H*H), 3.43 (1 H, m, N-CH), 4.03 (1 H, dd, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 5.6 Hz, CH), 7.56 and 8.16 (4 H, $^3J_{HH}$ = 7.8 Hz, $C_6H_4NO_2$), 8.03 (1 H, d, $^3J_{HH}$ = 7.7 Hz, NH), 12.21 (1 H, br s, CO_2H). ^{13}C NMR (DMSO-d_6): δ_C 24.81, 24.90, 25.63, 32.53 and 32.72 (5 CH_2), 37.47 (CH_2), 47.32 (N-CH), 48.13 (CH), 123.91, 129.30, 146.89 and 148.53 (arom.), 170.16 and 172.79 (2 C=O). MS (*m*/*z*, %) 321 (MH^+, 52), 303 (18), 221 (16), 195 (100), 153 (62), 83 (88). Anal. Calcd. for $C_{16}H_{20}N_2O_5$ (320.37): C, 59.98; H, 6.29; N, 8.74%. Found: C, 59.22; H, 6.17; N, 8.60%.

*4-(*t*-Butylamino)-3-(4-formylphenyl)-4-oxobutanoic acid* (**4c**): White crystals (0.230 g, 83%), m.p. 188–189°C (dec.). IR (KBr) ($\nu_{max,}$ cm^{-1}): 3300 (N–H), 2735 (OC–H), 2400–3400 (O-H), 1702 and 1637 (C=O). ^{1}H NMR (acetone-d_6): δ_H 1.25 (9 H, s, CMe_3), 2.59 (1 H, dd, $^2J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 5.5 Hz, CH*H*), 3.11 (1 H, dd, $^2J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 9.2 Hz, C*H*H), 4.01 (1 H, dd, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 5.5 Hz, CH), 7.01 (1 H, s, NH), 7.56 and 7.84 (4 H, $^3J_{HH}$ = 8.2 Hz, $C_6H_4NO_2$), 9.98 (1 H, s, CHO), 10.78 (1 H, br s, CO_2H). ^{13}C NMR (acetone-d_6): δ_C 28.34 (C*Me*$_3$), 37.80 (CH_2), 48.89 (CH), 51.06 (*C*Me$_3$), 128.81, 129.95, 135.96 and 147.69 (arom.), 171.19 and 172.29 (amide C=O and acid C=O), 192.00 (HC=O). MS (*m*/*z*, %) 278 (MH^+, 37), 178 (70), 133 (40), 57 (100). Anal. Calcd. for $C_{15}H_{19}NO_4$ (277.34): C, 64.96; H, 6.90; N, 5.05%. Found: C, 64.88; H, 6.92; N, 4.77%.

4-(Cyclohexylamino)-3-(4-formylphenyl)-4-oxobutanoic acid (**4d**): White crystals (0.264 g, 87%), m.p. 185–186°C (dec.). IR (KBr) ($\nu_{max,}$ cm^{-1}): 3270 (N-H), 2725 (OC-H), 2600–3400 (O-H), 1695 and 1633 (C=O). ^{1}H NMR (acetone-d_6): δ_H 1.26–1.69 (10 H, m, 5 CH_2), 2.65 (1 H, dd, $^2J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 5.5 Hz, CH*H*), 3.15 (1 H, dd, $^2J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 9.2 Hz, C*H*H), 3.63 (1 H, m, N–CH), 4.05 (1 H, dd, $^3J_{HH}$ = 9.2 Hz, $^3J_{HH}$ = 5.5 Hz, CH), 7.18 (1 H, d, $^3J_{HH}$ = 6.9 Hz, NH), 7.59 and 7.86 (4 H, 2d, $^3J_{HH}$ = 8.1 Hz, $C_6H_4NO_2$), 10.00 (1 H, s, CHO), 10.81 (1 H, br s, CO_2H). ^{13}C NMR (acetone-d_6): δ_C 25.03, 25.11, 25.80, 32.75 and 32.91 (5 CH_2), 37.65 (CH_2), 48.40 (N-CH), 48.64 (CH), 128.88, 129.93, 136.06 and 147.60 (arom.),

170.66 and 172.15 (amide C=O and acid C=O), 192.03 (HC=O). MS (*m*/*z*, %) 304 (MH^+, 5), 204 (3), 178 (100), 133 (60), 105 (12), 83 (37). Anal. Calcd. for $C_{17}H_{21}NO_4$ (303.38): C, 67.30; H, 6.97; N, 4.61%. Found: C, 67.09; H, 7.11; N, 4.53%.

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University.

Received 4 January 2002; accepted 18 April 2002
Paper 02/1193

References

1 A.N. Meldrum, *J. Chem. Soc*., 1908, **93**, 598.
2 A. Shaabani, I. Yavari, M.B. Teimouri, A. Bazgir and H.M. Bijanzadeh, *Tetrahedron*, 2001, **57**, 1375.
3 K. Kameo, K. Ogawa, K. Takeshita, S. Nakaike, K. Tomisawa and K. Sota, *Chem. Pharm. Bull*., 1988, **36**, 2050.
4 K. Tomisawa, K. Kameo, T. Matsunaga, S. Saito, K. Hosoda, Y. Asami and K. Sota, *Chem. Pharm. Bull*., 1985, **33**, 2386.
5 K. Kameo, K. Takeshita, Y. Yasuda, K. Matsumoto and K. Tomisawa, *Chem. Pharm. Bull*., 1996, **44**, 602.
6 A. Domling and I. Ugi, *Angew. Chem. Int. Ed*., 2000, **39**, 3168.
7 I. Ugi, *Isonitrile Chemistry*, Academic Press, 1971.
8 I. Yavari, A. Shaabani, and M.T. Maghsoodlou, *Monatsh. Chem*., 1997, **128**, 697.
9 I. Yavari, A. Shaabani, S. Asghari, M. Olmsted, and N. Safari, *J. Fluorine Chem*., 1997, **86**, 77.
10 A. Shaabani and F. Farrokhzad, *J. Chem. Research (S)*, 1997, 344.
11 A. Shaabani, S. Ajabi, F. Farrokhzad, and H.M. Bijanzadeh, *J. Chem. Research (S)*, 1999, 582.
12 J.D. Figueroa-Villar, C.L. Carneiro and E.R. Cruz, *Heterocycles*, 1992, **34**, 891.
13 J.A. Hedge, C.W. Kruse, and H.R. Snyder, *J. Org. Chem*., 1961, **26**, 3166.