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New and efficient synthesis of dialkyl 2-[1-*p*-nitrophenyl-2-(alkylamino)-2-oxoethyl]malonates

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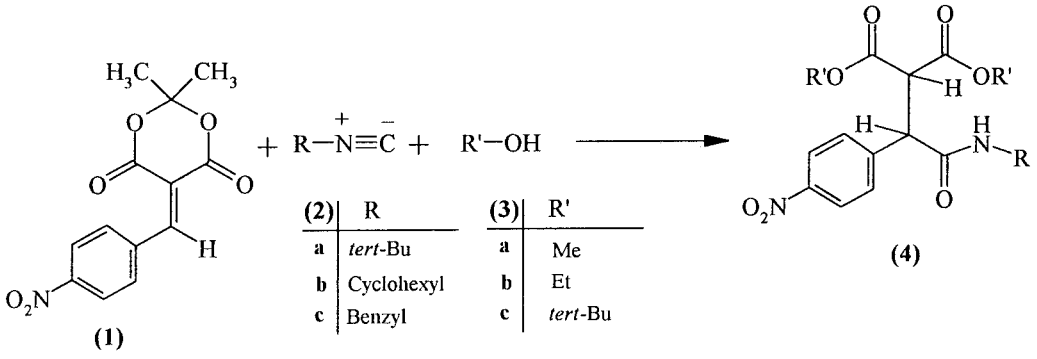
Abstract—The condensation product of Meldrum's acid and 4-nitrobenzaldehyde reacts smoothly with alkyl isocyanides in the presence of alcohols to produce dialkyl 2-[1-*p*-nitrophenyl-2-(alkylamino)-2-oxoethyl]malonates in excellent yield. This reaction provides a useful synthetic route to highly functionalized amidodiesters.

1. Introduction

Due to its great acidity (pK_a 7.5)[1] and tendency to regenerate acetone, Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione,[2] appears to be an attractive reagent in organic synthesis. However, synthetic applications of this acid have received little attention except as an alternative for acyclic malonic esters.[3] Recently, useful applications of alkylidene derivatives of Meldrum's acid as dienophiles have been reported, showing advantages of these compounds over



(4)	R	R'	(%)Yield
a	*tert*-Bu	Me	96
b	*tert*-Bu	Et	95
c	*tert*-Bu	*tert*-Bu	94
d	Cyclohexyl	Me	96
e	Cyclohexyl	Et	94
f	Cyclohexyl	*tert*-Bu	92
g	Benzyl	Et	93

Scheme 1.

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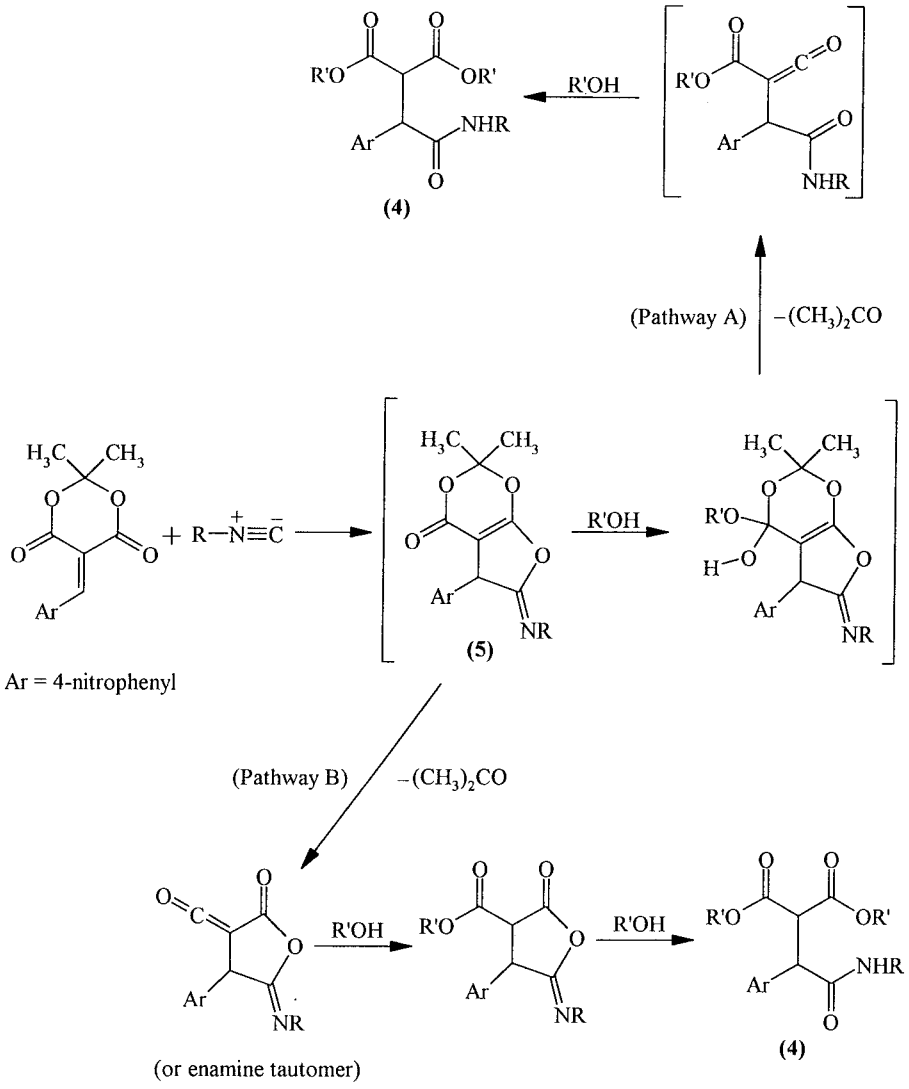

Scheme 2.

their acyclic analogues.[4–6] The present investigation was undertaken to develop the synthetic usefulness of the 4-nitrophenylmethylidene derivative of Meldrum's acid in the preparation of *N*-alkylamide derivatives of dialkyl malonates. Thus, reaction of alkyl isocyanides **2** with Meldrum's acid derivative **1** in the presence of alcohol **3** leads to the corresponding dialkyl 2-[1-*p*-nitrophenyl-2-(alkylamino)-2-oxoethyl]malonates **4** (Scheme 1).

2. Results and discussion

The reaction of alkylidene Meldrum's acid **1** with alkyl isocyanides **2** in the presence of an alcohol proceeded spontaneously at room temperature in 1:2 alcohol/dichloromethane, and finished within a few hours. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of dialkyl 2-[1-*p*-nitrophenyl-2-(alkylamino)-2-oxoethyl]-malonates **4**. Any product other than **4** could not be detected by NMR spectroscopy. The structures of compounds **4a–g** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. Any initial fragmentation involved the loss of ester moieties.

The ^{1}H NMR spectrum of **4a** exhibited three single sharp lines readily recognized as arising from *tert*-butyl (δ 1.28) and methoxy (δ 3.49 and 3.79) protons along with an AX system (J_{AX}=11.4 Hz) for two methine (δ 4.23 and 4.31) protons. A fairly broad singlet (δ 5.84) is observed for the NH group, and the 4-nitrophenylamino moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 13 distinct resonances in agreement with the amidoester structure. Partial assignment of these resonances is given in Section 3.

The ^{1}H and ^{13}C NMR spectra of **4b–g** are similar to those of **4a** except for the alkylamino and ester groups, which exhibit characteristic signals with appropriate chemical shifts (see Section 3).

We have not established a mechanism for the formation of dialkyl 2-[1-*p*-nitrophenyl-2-(alkylamino)-2-oxoethyl]malonates (**4**), but two reasonable possibilities are indicated in

Scheme 2. The first step of these mechanisms involves the [4+1] cycloaddition reaction of the electron-deficient heterodiene moiety of isopropylidene *p*-nitrobenzalmalonate with the isocyanide, an iminolactone intermediate. As it is known that acylated Meldrum's acids are readily transformed into β-ketoesters by alcoholysis,[6] the subsequent reaction of iminolactone **5** with alcohol leads to formation of product **4** (see pathway A in Scheme 2).

Since the reaction works well with *tert*-butyl alcohol as the alcohol component, the proposed addition to the vinylogous carbonate **5** in pathway A is expected to be slow. Thus, we prefer to suggest loss of acetone from **5** first and then sequential addition of R′OH to the so-formed ketene and the isourea[9] (see pathway B in Scheme 2).

In summary, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The one-pot nature of the present procedure makes it an interesting alternative to multistep approaches.[7] Further investigations of the present method will be required to establish its scope and limitations.

3. Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. 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 ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H 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 $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka Chemical Company (Buchs, Switzerland). Isopropylidene *p*-nitrobenzalmalonate was prepared according to a published procedure.[8]

3.1. General procedure

To a magnetically stirred solution of isopropylidene *p*-nitrobenzalmalonate (0.140 g, 0.5 mmol) in methanol (5 ml) and dichloromethane (10 ml) was added dropwise a solution of *tert*-butyl isocyanide (0.042 g, 0.5 mmol) in dichloromethane (2 ml) at 0°C over 10 min. The reaction mixture was allowed to warm up to room temperature and stirred for 5 h. The solution was concentrated to afford the white crystalline product. The product was filtered and washed with *n*-hexane and was recrystallized from 1:1 dichloromethane/*n*-hexane to yield the following compounds.

3.1.1. Dimethyl 2-[1-*p*-nitrophenyl-2-(*tert*-butylamino)-2-oxoethyl]malonate (4a). White crystals (0.176 g, 96%). Mp 199–200°C (dec.). IR (KBr) (ν_{max}, cm^{-1}): 3330 (N–H), 1745, 1734 and 1645 (C=O), 1541 and 1308 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.28 (9H, s, CMe_3), 3.49 and 3.79 (6H, 2s, $2OCH_3$), 4.23 and 4.31 (2H, 2d, $^3J_{HH}$=11.4 Hz, 2CH), 5.84 (1H, br s, NH), 7.60 and 8.18 (4H, 2d, $^3J_{HH}$=8.6 Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 28.41 (C*Me*$_3$), 51.77, 52.44, 52.72, 53.07 and 55.08 ($2OCH_3$, 2CH, *C*Me$_3$), 123.93 and 129.22 (4CH, arom.) 143.94 and 147.63 (2C, arom.), 167.89, 168.25 and 168.83 (3C=O). MS (*m*/*z*, %) 367 (MH^+, 25), 267 (80), 207 (44), 176 (38), 167 (75), 57 (100). Anal. Calcd for $C_{17}H_{22}N_2O_7$ (366.37): C, 55.73; H, 6.05; N, 7.65%. Found: C, 55.7; H, 6.1; N, 7.7%.

3.1.2. Diethyl 2-[1-*p*-nitrophenyl-2-(*tert*-butylamino)-2-oxoethyl]malonate (4b). White crystals (0.187 g, 95%). Mp 119–121°C. IR (KBr) (ν_{max}, cm^{-1}): 3385 (N–H), 1733, 1730 and 1669 (C=O), 1527 and 1339 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 0.99 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 1.27 (9H, s, CMe_3), 1.29 (3H, t, $^3J_{HH}$=7.2 Hz, CH_3), 3.94 (2H, ABX_3, J_{AX}=J_{BX}=7.2 Hz, J_{AB}=10.8 Hz, ν_A=3.92, ν_B=3.96, OCH_2), 4.22 (1H, d, $^3J_{HH}$=11.5 Hz, CH), 4.24 (2H, q, $^3J_{HH}$=7.2 Hz, OCH_2), 4.25 (1H, d, $^3J_{HH}$=11.5 Hz, CH), 5.86 (1H, br s, NH), 7.61 and 8.17 (4H, 2d, $^3J_{HH}$=8.5 Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 13.75 and 13.96 ($2CH_3$), 28.34 (C*Me*$_3$), 51.65 (*C*Me$_3$), 52.35 and 55.25 (2CH), 61.60 and 62.10 ($2OCH_2$), 127.75 and 129.30 (4CH, arom.), 144.05 and 147.50 (2C, arom.), 167.40, 167.85 and 168.82 (3C=O). MS (*m*/*z*, %) 395 (MH^+, 20), 349 (22), 295 (75), 222 (60), 176 (45), 57 (100), 41 (32). Anal. Calcd for $C_{19}H_{26}N_2O_7$ (394.42): C, 57.85; H, 6.65; N, 7.10%. Found: C, 57.9; H, 6.7; N, 7.2%.

3.1.3. Di-*tert*-butyl 2-[1-*p*-nitrophenyl-2-(*tert*-butylamino)-2-oxoethyl]malonate (4c). White crystals (0.211 g, 94%). Mp 214–215°C (dec.). IR (KBr) (ν_{max}, cm^{-1}): 3345 (N–H), 1738, 1699 and 1672 (C=O), 1519 and 1348 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.19, 1.26 and 1.47 (27H, 3s, $3CMe_3$), 3.97 and 4.05 (2H, 2d, $^3J_{HH}$=11 Hz, CH–CH), 5.55 (1H, s, NH), 7.58 and 8.17 (4H, 2d, $^3J_{HH}$=8 Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 27.58, 27.83 and 28.42 (3C*Me*$_3$), 51.70 and 52.59 (2CH), 57.10 (N*C*Me$_3$), 82.06 and 82.35 (2O*C*Me$_3$), 123.63 and 129.44 (4CH, arom.), 144.27 and 147.47 (2C, arom.), 166.50, 167.10 and 169.19 (3C=O). MS (*m*/*z*, %) 450 (M^+, 1) 377 (32), 321 (38), 239 (42), 195 (80), 57 (100). Anal. Calcd for $C_{23}H_{34}N_2O_7$ (450.52): C, 61.31; H, 7.61; N, 6.22%. Found: C, 61.2; H, 7.7; N, 6.3%.

3.1.4. Dimethyl 2-[1-*p*-nitrophenyl-2-(cyclohexylamino)-2-oxoethyl]malonate (4d). White crystals (0.188 g, 96%). Mp 197–199°C (dec.). IR (KBr) (ν_{max}, cm^{-1}): 3380, 3350 (N–H), 1735, 1637 (C=O), 1510 and 1346 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 0.90–1.90 (10H, m, $5CH_2$), 3.49 (3H, s, OCH_3), 3.68 (1H, m, N–CH), 3.78 (3H, s, OCH_3), 4.20 (1H, d, $^3J_{HH}$=11 Hz, CH), 4.33 (1H, d, $^3J_{HH}$=11 Hz, CH), 5.68 (1H, d, $^3J_{HH}$=7 Hz, NH), 7.57 and 8.17 (4H, 2d, $^3J_{HH}$=8 Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.68, 24.75, 25.41, 32.55 and 32.77 ($5CH_2$), 48.94 (N–*C*H), 52.01 and 55.00 (2CH), 52.74 and 53.11 ($2OCH_3$), 123.95, 129.31 (4CH, arom.), 143.62 and 147.70 (2C, arom.), 167.71, 168.12 and 168.69 (3C=O). MS (*m*/*z*, %) 392 (M^+, 25), 361 (52), 329 (22), 294 (24), 267 (100), 207 (72), 176 (50), 83(36), 55 (24). Anal. Calcd for $C_{19}H_{24}N_2O_7$ (392.40): C, 58.15; H, 6.16; N, 7.14%. Found: C, 58.0; H, 6.1; N, 7.2%.

3.1.5. Diethyl 2-[1-*p*-nitrophenyl-2-(cyclohexylamino)-2-oxoethyl]malonate (4e). White crystals (0.197 g, 94%). Mp 126–127°C. IR (KBr) (ν_{max}, cm^{-1}): 3316 (N–H), 1736,

1720 and 1645 (C═O), 1515 and 1343 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 0.99 and 1.29 (6H, 2t, $^3J_{HH}$=7 Hz, $2CH_3$), 1.05–1.25 and 1.5–2.0 (10H, m, $5CH_2$), 3.67 (1H, m, N–CH), 3.95 and 4.25 (4H, 2ABX$_3$ system, $2OCH_2$), 4.32 (2H, AB system, J_{AB}=11 Hz, CH–CH), 6.16 (1H, d, $^3J_{HH}$=8 Hz, NH), 7.63 and 8.17 (4H, 2d, $^3J_{HH}$=8 Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 13.54 and 13.58 ($2CH_3$), 24.60, 24.75, 25.38, 32.40 and 32.66 ($5CH_2$), 48.90 (N–*C*H), 51.26 and 52.32 ($2OCH_3$), 54.51 and 55.52 (2CH), 61.65 and 62.06 ($2OCH_2$), 123.72, 129.40 (4CH, arom.), 144.00 and 147.62 (2C, arom.), 167.35, 167.80 and 168.75 (3C═O). MS (*m*/*z*, %) 421 (MH^+, 26), 375 (15), 295 (100), 222 (85), 83 (42), 55 (74). Anal. Calcd for $C_{21}H_{28}N_2O_7$ (420.44): C, 59.98; H, 6.71; N, 6.66%. Found: C, 60.1; H, 6.8; N, 6.7%.

3.1.6. Di-*tert*-butyl 2-[1-*p*-nitrophenyl-2-(cyclohexylamino)-2-oxoethyl]malonate (4f). White crystals (0.219 g, 92%). Mp 194–196°C (dec.). IR (KBr) (ν_{max}, cm^{-1}): 3350 (N–H), 1743, 1688 and 1668 (C═O), 1514 and 1348 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 0.90–1.90 (10H, m, $5CH_2$), 1.18 and 1.46 (18H, 2s, $2CMe_3$), 3.66 (1H, m, N–CH), 4.08 and 4.14 (2H, 2d, $^3J_{HH}$=11 Hz, CH–CH), 5.85 (1H, d, $^3J_{HH}$=8 Hz, NH), 7.61 and 8.15 (4H, 2d, $^3J_{HH}$=8 Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.73, 24.78, 25.46 ($3CH_2$), 27.57, 27.88 ($2CMe_3$), 32.59 and 32.71 ($2CH_2$), 48.87 (N–*C*H), 51.95 and 56.88 (2CH), 82.08 and 82.41 ($2CMe_3$), 123.56, 129.70 (4CH, arom.), 144.25 and 147.47 (2C, arom.), 166.64, 167.13 and 169.11 (3C═O). MS (*m*/*z*, %) 477 (MH^++1, 22), 421 (30), 365 (55), 239 (38), 195 (100), 57 (95). Anal. Calcd for $C_{25}H_{36}N_2O_7$ (476.56): C, 63.00; H, 7.61; N, 5.88%. Found: C, 62.9; H, 7.6; N, 5.9%.

3.1.7. Diethyl 2-[1-*p*-nitrophenyl-2-(benzylamino)-2-oxoethyl]malonate (4g). White crystals (0.199 g, 93%). Mp 125–127°C. IR (KBr) (ν_{max}, cm^{-1}): 3390 (N–H), 1729 and 1645 (C═O), 1514 and 1379 (NO_2). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 0.98 and 1.27 (6H, 2t, $^3J_{HH}$=7 Hz, $2CH_3$), 3.92 (2H, ABX$_3$ system, OCH_2), 4.22 (2H, ABX$_3$ system, OCH_2), 4.24 and 4.33 (2H, 2d, $^3J_{HH}$=11 Hz, CH–CH), 4.33 and 4.46 (2H, 2dd, $^2J_{HH}$=15 Hz, $^3J_{HH}$= 6 Hz, NCH_2), 6.10 (1H, t, $^3J_{HH}$=6 Hz, NH), 7.10–7.60 (5H, m, C_6H_5), 7.63 and 8.23 (4H, 2d, $^3J_{HH}$=8 Hz, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 13.68 and 13.84 ($2CH_3$), 43.49 (NCH_2), 51.51 and 54.97 (2CH), 61.73 and 62.18 ($2OCH_2$), 123.67 (2CH, C_6H_4), 127.13 (C_{para}, C_6H_5), 127.14 and 128.43 (C_{meta} and C_{ortho}, C_6H_5), 138.00 (C_{ipso}, C_6H_5), 143.66 and 147.45 (2C, C_6H_4), 167.53, 167.89 and 170.36 (3C═O). MS (*m*/*z*, %) 428 (M^+, 10), 222 (20), 193 (16), 176 (22), 91 (100). Anal. Calcd for $C_{22}H_{24}N_2O_7$ (428.43): C, 61.67; H, 5.65; N, 6.54%. Found: C, 61.6; H, 5.7; N, 6.4%.

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9. We are grateful to the referee of this paper for proposing pathway B.