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An efficient synthesis of amidodiester derivatives via a *pseudo* five-component one-pot reaction under solvent-free conditions

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Abstract: We reported a green, simple and efficient method for the synthesis of amidodiester derivatives employing a multi-component and one-pot condensation reaction of between Meldrum's acid, aryl aldehydes with alkyl isocyanide in the presence of two equivalents alcohols under solvent-free conditions at room temperature. This new protocol offers advantages such as *pseudo* five-component one-pot reaction, aerobic conditions, milder reaction conditions without additives, high yields, easy work-up and does not involve any hazardous solvent. Therefore, this procedure could be classified as green chemistry. To Meldrum's acid at r.t. was added aryl aldehyde. The reaction mixture was stirred for 5 min. Then, alcohols was added at this temperature. Reaction mixture was then stirred for one minute, alkyl isocyanide was added and the reaction mixture was stirred for more 24h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, The viscose oil yellow was collected and to afford the pure title compounds. The structures of compounds were deduced from elemental analysis and their IR, ^{1}H NMR, ^{13}C NMR spectra.

Keywords: Solvent-free, Meldrum's acid, Isocyanides, Amidodiesters, Green chemistry.

Introduction

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity[1]. In the recent years, chemistry of Meldrum's acid derivatives has attracted much attention owing to their potential synthetic utility and diversity of reactions[2,3]. These compounds are useful intermediates in cycloaddition reactions not only as good dienophiles but also as good oxy-dienes in hetero-Diels–Alder reactions[4-7]. Synthesis of amidodiester derivatives has already been reported in the presence of 1:2 methanol /dichloromethane at room temperature [8].

We now report a simple one-pot method for synthesis of amidodiester derivatives under solvent-free conditions at room temperature and have synthesised to another class of amidodiester derivatives via a *pseudo* five-component one-pot reaction. In the context of our recent studies [9-12] on the reactivity of Meldrum's acid, we studied the reaction between Meldrum's acid, aryl aldehydes with alkyl isocyanide in the presence of two equivalents alcohols under solvent-free conditions at room temperature.

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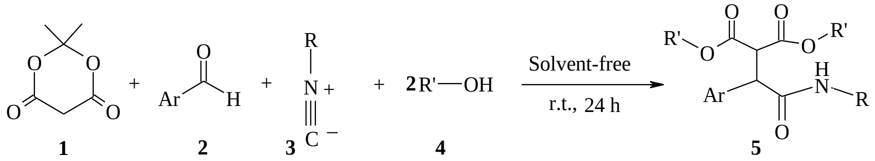
Result and Discussion

The reaction of Meldrum's acid **1** and aryl aldehydes **2** with alkyl isocyanide **3** in the presence of alcohols **4** leds to amidodiester derivatives **5** in good yields (Scheme **1**).

The compounds **5a-g** were characterised by their ^{1}H-NMR and IR spectroscopy and elemental analyses. Spectral data were compared with the literature data [8]. Compounds **5h-l** was new and their structures were deduced by their ^{1}H, ^{13}C-NMR and IR spectroscopy and elemental analyses (Table **1**).

The ^{1}H-NMR spectrum of **5h** exhibited three single sharp lines readily recognized as arising from tert-butyl (δ= 1.30) and methoxy (δ = 3.42 and 3.76) protons along with an AX system (J_{AX} =11.4 Hz) for two methine (δ = 4.01 and 4.22) protons. A broad singlet (δ = 5.32) is observed for the NH group, and the aromatic region are observed at δ = 7.26-7.30 ppm. The ^{13}C-NMR spectrum of **5h** showed 13 distinct resonances in agreement with the amidoester structure.

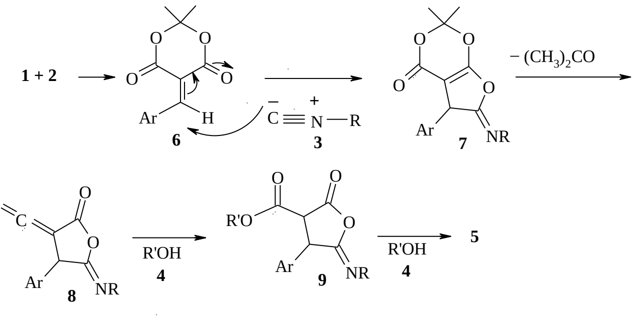


Scheme 1: Synthesis of amidodiester derivatives via a *pseudo* five-component one-pot reaction under solvent-free conditions

Table 1: Yields of a series of amidodiester derivatives (**5**) (Scheme **1**)

Product	Ar	R	R'	Yield (%)[a]	m.p. (° C)	
					found	reported
5a	4-NO_2-C_6H_4	*t*-Bu	Me	93	200-202	199-200 (Ref.8)
5b	4-NO_2-C_6H_4	*t*-Bu	Et	91	118-120	119-121 (Ref.8)
5c	4-NO_2-C_6H_4	*t*-Bu	*t*-Bu	90	215-217	214-215 (Ref.8)
5d	4-NO_2-C_6H_4	Cyclohexyl	Me	91	198-200	197-199 (Ref.8)
5e	4-NO_2-C_6H_4	Cyclohexyl	Et	89	125-127	126-127 (Ref.8)
5f	4-NO_2-C_6H_4	Cyclohexyl	*t*-Bu	88	196-197	194-196 (Ref.8)
5g	4-NO_2-C_6H_4	$C_6H_5CH_2$	Et	90	126-128	125-127 (Ref.8)
5h	C_6H_5	*t*-Bu	Me	88	Oil	-
5i	C_6H_5	*t*-Bu	*iso*-Pro	80	Oil	-
5j	4-Cl-C_6H_4	*t*-Bu	Me	85	Oil	-
5k	4-Cl-C_6H_4	*t*-Bu	*iso*-Pro	81	Oil	-
5l	4-NO_2-C_6H_4	*t*-Bu	*iso*-Pro	85	Oil	-

The compounds **5a-g** was characterized by their ^{1}H-NMR and IR spectroscopy and elemental analysis. Spectral data were compared with the literature data [8]. Compounds **5h-l** was new and their structures were deduced by their ^{1}H, ^{13}C-NMR and IR spectroscopy and elemental analysis (Table **1**). The ^{1}H-NMR spectrum of **5h** exhibited three single sharp lines readily recognized as arising from tert-butyl (δ= 1.30) and methoxy (δ = 3.42 and 3.76) protons along with an AX system (J_{AX} =11.4 Hz) for two methine (δ = 4.01 and 4.22) protons. A broad singlet (δ = 5.32) is observed for the NH group, and the aromatic region are observed at δ = 7.26-7.30 ppm. The ^{13}C-NMR spectrum of **5h** showed 13 distinct resonances in agreement with the amidoester structure.The mechanism of the reaction is probably similar to that published by Shaabani *et al.*[8] (Scheme **2**).



Scheme 2 Suggested mechanism for formation of compound **5**

Conclusions

In conclusion, we reported the four-component reaction between Meldrum's acid, aryl aldehydes with alkyl isocyanide in the presence of two equivalents alcohols under solvent-free conditions at room temperature leads to amidodiester derivatives in high yields. The salient features of this protocol are *pseudo* five-component one-pot reaction, aerobic conditions, nonhazardous, green catalyst, milder reaction conditions without additives and high yields. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified as green chemistry.

Experimental

General. Isopropylidene Meldrum's acid was prepared by addition of Meldrum's acid to acetone in presence of piperidine and glacial acetic acid [6]. Melting points were measured on an *Electrothermal 9100* apparatus. Further purification. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H-and ^{13}C-NMR spectra: *Bruker DRX-500 AVANCE* instrument; in CDCl$_3$ at 500.1 and 125.7 MHz, resp; δ in ppm, *j* in Hz. EI-MS (70 eV): *Finnigan-MAT-8430* mass spectrometer, in m/z. Elemental analysis (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer.

General procedure for preparation of compounds **5a-l**:

To Meldrum's acid (1 mmol) at r.t. was added aryl aldehyde (1 mmol). The reaction mixture was stirred for 5 min. Then, alcohols (2 mmol) was added at this temperature. Reaction mixture was then stirred for one minute, alkyl isocyanide (1 mmol) was added and the reaction mixture was stirred for more 24h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, The viscose oil yellow was collected and washed with 10 ml of cold diethyl ether to afford the pure title compounds.

Dimethyl 2-[phenyl-2-(tert-butylamino)-2-oxoethyl]malonate **(5h):**

Yellow viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 3332 (NH), 1760 and 1643 (C=O); ^{1}HNMR (CDCl$_3$, Me$_4$Si): δ 1.30 (9H, s, CMe$_3$), 3.42 and 3.76 (6H, 2s, 2OCH$_3$), 4.01 and 4.22 (2H, 2d, $^3J_{HH}$ = 11.4Hz, 2CH), 5.32 (1H, br s, NH), 7.26-7.30 (5H, m, aromtic) ppm. ^{13}CNMR (CDCl$_3$, Me$_4$Si): δ 28.32 (CMe$_3$), 51.48, 52.42, 52.73, 52.84 and 55.25 (2OCH$_3$, 2CH, CMe$_3$), 127.45, 128.65, 129.79 and 136.32 (aromatic), 168.30, 168.67 and 170.17 (3C=O) ppm.; MS (m/z, %): 321 (M, 7); Anal. calcd. For $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36%. Found: C, 63.71; H, 7.35; N, 4.47.

Di-iso-propyl 2-[phenyl-2-(tert-butylamino)-2-oxoethyl]malonate **(5i):**

Yellow viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 3396 (NH), 1724 and 1675 (C=O); ^{1}HNMR (CDCl$_3$, Me$_4$Si): δ 0.92-1.29 (12H, d, $^3J_{HH}$=6.5 Hz, 2CHMe$_2$), 1.29 (9H, s, CMe$_3$), 3.93 and 4.13 (2H, 2d, $^3J_{HH}$ = 11.4Hz, 2CH), 4.70-5.06 (2H, m, 2CHMe$_2$), 5.33 (1H, br s, NH), 7.26-7-34 (5H, m, aromtic) ppm. ^{13}CNMR (CDCl$_3$, Me$_4$Si): δ 21.43 and 21.80 (2CHMe$_2$), 28.47 (CMe$_3$), 51.37, 52.70 and 55.73 (CMe$_3$, 2CH), 69.24 and 69.74 (2CHMe$_2$), 127.76, 128.66, 129.73 and 136.50 (aromatic), 167.40, 167.87 and 170.31 (3C=O)ppm.; MS (m/z, %): 377 (M, 3); Anal. calcd. For $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71%. Found: C, 66.65; H, 8.40; N, 3.89.

Dimethyl 2-[1-p-clorophenyl-2-(tert-butylamino)-2-oxoethyl]malonate **(5j):**

Yellow viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 3327 (NH), 1740 and 1643 (C=O); ^{1}HNMR (CDCl$_3$, Me$_4$Si): δ 1.33 (9H, s, CMe$_3$), 3.43 and 3.75 (6H, 2s, 2OCH$_3$), 3.96 and 4.15 (2H, 2d, $^3J_{HH}$ = 11.4Hz, 2CH), 5.82 (1H, br s, NH), 7.21-7.41 (4H, m, aromtic) ppm. ^{13}CNMR (CDCl$_3$, Me$_4$Si): δ 28.34 (CMe$_3$), 50.34, 51.50, 51.86, 52.57 and 55.10 (2OCH$_3$, CMe$_3$, 2CH), 128.95, 129.42, 133.81 and 134.87 (aromatic), 168.20, 168.48 and 169.85 (3C=O) ppm.; MS (m/z, %): 355 (M, 10); Anal. calcd. For $C_{17}H_{22}ClNO_5$: C, 57.39; H, 6.23; N, 3.94%. Found: C, 57.52; H, 6.05; N, 4.11.

Di-iso-propyl 2-[1-p-clorophenyl-2-(tert-butylamino)-2-oxoethyl]malonate **(5k):**

Yellow viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 3336 (NH), 1742 and 1645 (C=O); ^{1}HNMR (CDCl$_3$, Me$_4$Si): δ 0.95-1.32 (12H, d, $^3J_{HH}$ = 6.5 Hz, 2CHMe$_2$), 1.31 (9H, s, CMe$_3$), 3.90 and 4.18 (2H, 2d, $^3J_{HH}$ = 11.4Hz, 2CH), 4.65-5.02 (2H, m, 2CHMe$_2$), 5.30 (1H, br s, NH), 7.23-7.42 (4H, m, aromtic) ppm. ^{13}CNMR (CDCl$_3$, Me$_4$Si): δ 21.40 and 21.85 (2CHMe$_2$), 28.65 (CMe$_3$), 51.33, 52.64 and 55.64 (CMe$_3$, 2CH), 69.28 and 69.80 (2CHMe$_2$), 128.92, 129.47, 133.74 and 134.81 (aromatic), 167.45, 167.91 and 170.38 (3C=O)ppm.; MS (m/z, %): 411 (M, 5); Anal. calcd. For $C_{21}H_{30}ClNO_5$: C, 61.23; H, 7.34; N, 3.40%. Found: C, 61.42; H, 7.21; N, 3.51.

Di-iso-propyl 2-[1-p-nitrophenyl-2-(tert-butylamino)-2-oxoethyl]malonate **(5l):**

Yellow viscous oil, IR (KBr) (ν_{max}, cm^{-1}): 3381 (NH), 1534 and 1331 (NO$_2$), 1735 and 1664 (C=O); ^{1}HNMR (CDCl$_3$, Me$_4$Si): δ 1.03-1.40 (12H, d, $^3J_{HH}$ = 6.5 Hz, 2CHMe$_2$), 1.29 (9H, s, CMe$_3$), 4.19 and 4.27 (2H, 2d, $^3J_{HH}$ = 11.4Hz, 2CH), 4.60-5.11 (2H, m, 2CHMe$_2$), 5.72 (1H, br s, NH), 7.56-8.11 (4H, m, aromtic) ppm. ^{13}CNMR (CDCl$_3$, Me$_4$Si): δ 21.32 and 21.74 (2CHMe$_2$), 28.37 (CMe$_3$), 51.57, 52.32 and 52.44 (CMe$_3$, 2CH), 69.14 and 69.75 (2CHMe$_2$), 127.63, 129.34, 144.15 and 147.37 (aromatic), 167.31, 167.80 and 168.71 (3C=O)ppm.; MS (m/z, %): 422 (M, 8); Anal. calcd. For $C_{21}H_{30}N_2O_7$: C, 59.70; H, 7.16; N, 6.63%. Found: C, 59.83; H, 7.03; N, 6.80.

Acknowledgements

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