JOC Article

Facile Synthesis of α-Substituted Acrylate Esters

Bunda Hin, Pavel Majer, and Takashi Tsukamoto*

Guilford Pharmaceuticals, Inc., 6611 Tributary Street, Baltimore, Maryland 21224

tsukamotot@guilfordpharm.com

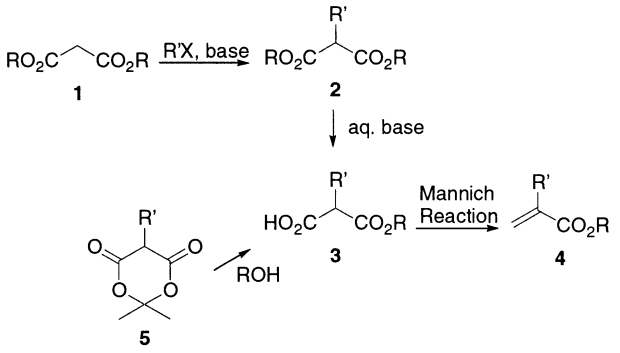
Received June 25, 2002

Treatment of 5-monosubstituted Meldrum's acids with dimethylmethyleneimmonium iodide (Eschenmoser's iodide salt) in methanol gives α-substituted acrylate methyl esters in good yields. Easy access to 5-monosubstituted Meldrum's acids allowed us to synthesize a wide variety of α-substituted acrylate methyl esters. The reaction conditions are mild and tolerate many functional groups commonly used in organic synthesis; thus, this new method has potential as an alternative to conventional preparative methods for α-substituted acrylate esters.

Introduction

Utility of α-substituted acrylate esters as synthetic intermediates has been well demonstrated by the 1,4-addition reaction of various types of nucleophilic reagents leading to several biologically important compounds. For example, 1,4-addition reactions of phosphorus-based nucleophiles to α-substituted acrylate esters have been extensively used in the synthesis of pseudopeptides including inhibitors of metalloproteases[1−3] and ATP-dependent ligases.[4−6] One of the most common methods for the acrylate synthesis involves a Mannich reaction of α-monosubstituted malonic acid half esters **3** (Scheme 1).[7] Although the reaction generally gives the products **4** in good yields, preparation of the starting materials **3** often suffers from low yield due to difficulties in monoalkylation of malonate diesters **1** and/or partial saponification of the monosubstituted malonate diesters **2**. It has been described, however, that the α-monosubstituted malonic acid esters **3** can be readily obtained by heating an alcoholic (phenol,[8] methanol,[9] ethanol,[10,11] benzyl alcohol,[12,13] or *tert*-butyl alcohol[14]) solution of 5-monosubstituted Meldrum's acids **5**. Recent progress in the practical synthesis of 5-monosubstituted Meldrum's acids[15−23] should enhance the utility of this alcoholysis reaction as a new route to α-monosubstituted malonic acid half esters. Since the alcoholysis of 5-monosubstituted Meldrum's acids **5** proceeds under mild conditions, this reaction could be combined with the subsequent Mannich reaction. In this paper, we describe a one-pot procedure for the preparation of α-substituted acrylate esters from 5-monosubstituted Meldrum's acids.

SCHEME 1



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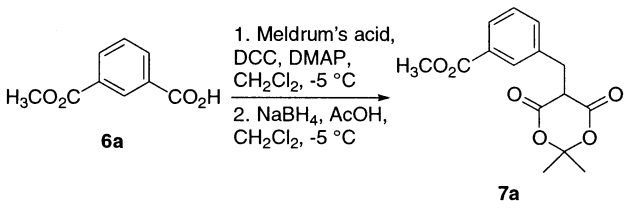
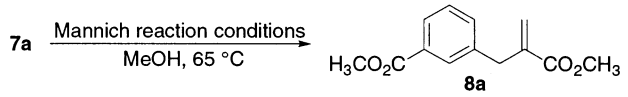
10.1021/jo026101s CCC: $22.00
Published on Web 09/24/2002

SCHEME 2



SCHEME 3



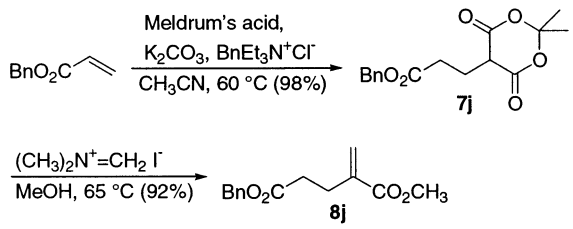
Results and Discussion

5-Monosubstituted Meldrum's acids, key materials for this synthetic study, can be readily prepared from Meldrum's acid and carboxylic acids by using a previously reported method.[17] Thus, DCC-mediated coupling of isophthalic acid monomethylester **6a** to Meldrum's acid followed by reduction with sodium borohydride afforded compound **7a** in 75% yield (Scheme 2). Using compound **7a** as a substrate and methanol as a solvent, we evaluated various different Mannich reaction conditions (Scheme 3). In most cases (e.g., diethylamine and formaldehyde), acrylate methyl ester **8a** was obtained as a major product even though ^{1}H NMR analyses of the crude materials indicate the formation of other minor products. Several reaction conditions were evaluated, and dimethylmethyleneimmonium iodide[24] (Eschenmoser's iodide salt) produced the best results. In fact, when a solution of **7a** in methanol was stirred at 65 °C in the presence of Eschenmoser's iodide salt, the desired compound **8a** was obtained as the sole product in 95% yield.

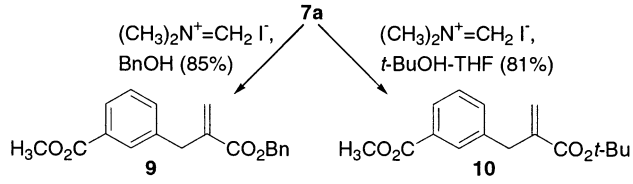
To explore the scope and utility of this reaction, we prepared a variety of 5-monosubstituted Meldrum's acids **7a**−**j**, which were subsequently converted into α-substituted acrylate methyl esters **8a**−**j** using this new method. The results are summarized in Table 1. In all cases, the reaction provides the products in good yields (72−98%). The reaction conditions are mild and tolerate many functional groups commonly used in organic synthesis. For example, *S*-triphenylmethyl thioether, *tert*-butyl carbamate, and benzyl and *tert*-butyl esters remained intact under the reaction conditions. This allowed us to prepare more complex molecule **8h**, a fully protected derivative of (*R*)-2-amino-6-methyleneheptanedioic acid. Although similar compounds have been previously synthesized in multiple steps for the purpose of studying the diaminopimelate (DAP) pathway,[25,26] our route requires fewer steps and offers higher total yield from commercially available materials.

In addition to the method described in Scheme 2, there are several other practical synthetic methods for 5-monosubstituted Meldrum's acids,[18−23] which would provide access to a wider range of α-substituted acrylate esters by combining with our new acrylate synthetic method.

SCHEME 4



SCHEME 5



For example, Michael addition of benzyl acrylate to Meldrum's acid gives 3-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propionic acid benzyl ester **7j** (Scheme 4). The compound **7j** was subsequently converted into differentially protected 2-methyleneglutarate derivative **8j**, which is not accessible by direct dimerization of acrylate esters.

As an extension to this methodology, we speculated that we could introduce other ester groups by changing solvent from methanol to other alcohols. Thus, compound **7a** was treated with Eschenmoser's iodide salt in benzyl alcohol or *tert*-butyl alcohol (with THF as a cosolvent). In both cases, the reactions proceeded smoothly while the original benzoate methyl ester group remained intact, providing orthogonally protected α-substituted acrylate benzyl ester **9** and *tert*-butyl ester **10**, respectively (Scheme 5). This modification provides additional value to our method since these acrylate esters have not been prepared through the conventional approach in Scheme 1 due to difficulty in obtaining malonic acid monobenzyl and mono-*tert*-butyl esters by direct hydrolysis of the corresponding diesters.

Conclusion

We have developed a highly efficient method for the one-pot synthesis of α-substituted acrylate esters from the corresponding 5-monosubstituted Meldrum's acids. We demonstrated that the new method provides a wide variety of α-substituted acrylate esters in high yields. The mild conditions, simple procedure, clean reaction, and high yields of the products coupled with ready access to various 5-monosubstituted Meldrum's acids make the present method a very attractive alternative to the previously known methods for the synthesis of α-substituted acrylate esters.

Experimental Section

General Methods. All reactions were performed under nitrogen. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 or 400 MHz and ^{13}C NMR spectra at 75 or 100 MHz. Elemental analyses were obtained from Atlantic Microlabs, Norcross, GA. The preparation of (*R*)-5-[(2-*tert*-butoxycarbonylamino-3-methyl)butyl]-2,2-dimethyl-1,3-dioxane-4,6-dione **(7f)** and (*R*)-5-

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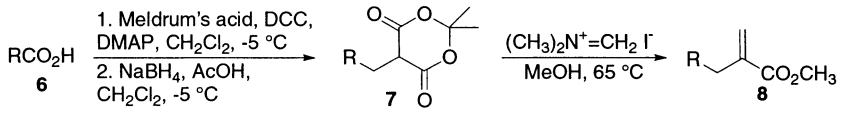
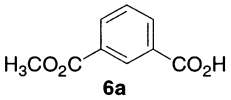
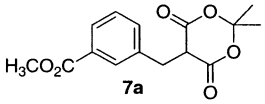
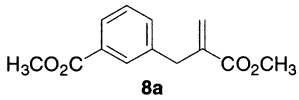
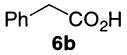
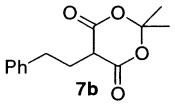
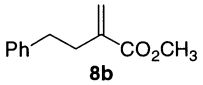
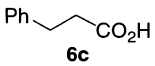
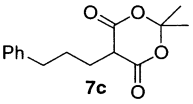
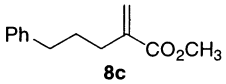
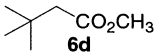
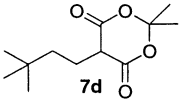
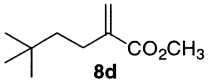
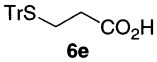
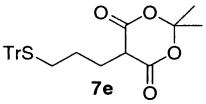
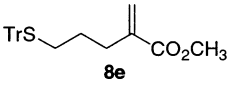
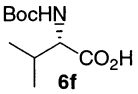
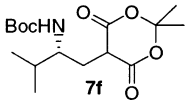
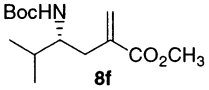
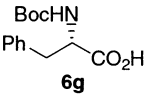
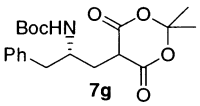
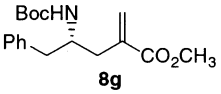
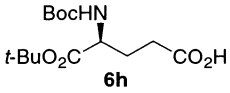
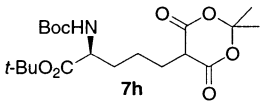
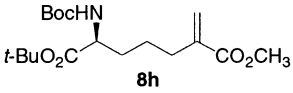
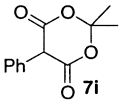
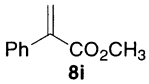
TABLE 1. Synthesis of α-Substituted Acrylate Methyl Esters from Carboxylic Acids



entry	carboxylic acid **6**	compound **7**	yield	compound **8**	yield
1	 **6a**	 **7a**	75%	 **8a**	95%
2	 **6b**	 **7b**	94%	 **8b**	91%
3	 **6c**	 **7c**	68%	 **8c**	84%
4	 **6d**	 **7d**	78%	 **8d**	73%
5	 **6e**	 **7e**	75%	 **8e**	98%
6	 **6f**	 **7f**	76%[a]	 **8f**	83%
7	 **6g**	 **7g**	78%[a]	 **8g**	82%
8	 **6h**	 **7h**	80%	 **8h**	80%
9		 **7i**	N/A[b]	 **8i**	72%

[a] Reference 17. [b] Commercially available.

[(2-*tert*-butoxycarbonylamino-3-phenyl)propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione **(7g)** has been previously described.[17]

General Procedure for the Preparation of 5-Monosubstituted Meldrum's Acids: 3-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylmethyl)benzoic Acid Methyl Ester (7a). A solution of DCC (4.74 g, 23 mmol) in dichloromethane (50 mL) was added to a solution of carboxylic acid **6a** (3.60 g, 20 mmol), Meldrum's acid (3.20 g, 22 mmol), and DMAP (3.85 g, 32 mmol) in dichloromethane (100 mL) at 0 °C over a period of 1 h. The reaction mixture was kept at 0 °C overnight, and the resulting white precipitate (dicyclohexylurea, DCU) was removed by filtration. The filtrate was washed with aq 10% $KHSO_4$ (100 mL × 4) and brine (100 mL) and then dried over $MgSO_4$. The solution was acidified by acetic acid (13.5 mL) at 0 °C, and $NaBH_4$ (1.85 g, 50 mmol) was added over a period of 1 h. The reaction mixture was kept at 0 °C overnight, washed with brine (100 mL × 2) and water (100 mL × 2), dried over $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by recrystallization from EtOAc/hexanes to give 4.40 g of **7a** as a white solid (75% yield): mp 129−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.75 (s, 3H), 3.50 (d, J = 5.2 Hz, 2H), 3.80 (t, J = 5.2 Hz 1H), 3.89 (s, 3H), 7.33−7.39 (m, 1H), 7.52−7.57 (m, 1H), 7.88−7.92 (m, 1H), 7.96−7.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 28.3, 31.5, 47.9, 52.0, 105.1, 128.2, 128.5, 130.3, 130.5, 134.3, 137.7, 164.9, 166.8. Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.89; H, 5.52. 5-Monosubstituted Meldrum's acids **7b**−**h** were prepared using the same procedure and purified by either recrystallization from EtOAc/hexanes (**7e**−**h**) or silica gel chromatography using EtOAc/hexanes as eluent (**7b**−**d**). The product characterization data for compounds **7b**−**h** are provided in Supporting Information.

3-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propionic Acid Benzyl Ester (7j). To a solution of Meldrum's acid (1.44 g, 10 mmol) in acetonitrile (15 mL) were added K_2CO_3 (1.38 g, 10 mmol, 1.0 equiv) and benzyltriethylammonium chloride (2.28 g, 10 mmol, 1.0 equiv) at rt. The suspension was stirred at rt for 15 min, and benzyl acrylate (2.43 g, 15 mmol, 1.5 equiv) was added to the suspension at rt. The resulting mixture was stirred at 60 °C for 12 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (50 mL). The organic solution was washed with aq 10%

$KHSO_4$ (50 mL × 3), dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 3:7) to give 3.0 g of **7j** as a white solid (98% yield): mp 56−57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 3H), 1.74 (s, 3H), 2.34−2.43 (m, 2H), 2.68 (t, J = 7.2 Hz, 2H), 3.88 (t, J = 5.6 Hz, 1H), 5.10 (s, 2H), 7.28−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 26.3, 28.4, 30.3, 44.7, 66.4, 105.0, 128.2, 128.3, 128.5, 135.6, 165.0, 172.6. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 63.03; H, 5.89.

General Procedure for the Synthesis of α-Substituted Acrylate Methyl Esters: 3-(2-Methoxycarbonylallyl)-benzoic Acid Methyl Ester (8a). A solution of 5-monosubstituted Meldrum's acid **7a** (0.125 g, 0.43 mmol) and dimethyl methyleneimmonium iodide (0.20 g, 1.1 mmol, 2.5 equiv) in anhydrous methanol (5 mL) was stirred at 65 °C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in diethyl ether (15 mL). The organic solution was washed with aq saturated $NaHCO_3$ (15 mL), aq 10% $KHSO_4$ (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated to give 0.096 g of **8a** as a colorless oil (95% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 2H), 3.73 (s, 3H), 3.90 (s, 3H), 5.50 (s, 1H), 6.27 (s, 1H), 7.40−7.48 (m, 2H), 7.85−7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.7, 51.7, 51.9, 126.6, 127.5, 128.3, 129.9, 130.1, 133.5, 138.9, 139.3, 166.8, 166.9. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.67; H, 6.02. Found: C, 66.59; H, 6.05. α-Substituted acrylate methyl esters **8b**−**j** were prepared using the same procedure. The product characterization data for compounds **8b**−**j** are provided in Supporting Information.

3-(2-Benzyloxycarbonylallyl)benzoic Acid Methyl Ester (9). A solution of **7a** (0.30 g, 1.0 mmol) and dimethylmethyleneimmonium iodide (0.49 g, 2.6 mmol) in benzyl alcohol (3 mL) was stirred at 65 °C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in diethyl ether (15 mL). The organic solution was washed with aq saturated $NaHCO_3$ (15 mL), aq 10% $KHSO_4$ (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residual oil was purified by silica gel column chromatography (EtOAc/hexanes, 3:7) to give 0.27 g of **9** as a colorless oil (85% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 2H), 3.89 (s, 3H), 5.15 (s, 2H), 5.52 (s, 1H), 6.32 (s, 1H), 7.25−7.40 (m, 7H), 7.86−7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9, 52.0, 66.5, 127.1, 127.7, 128.0, 128.1, 128.4, 130.0, 130.2, 133.6, 135.7, 139.0, 139.4, 166.3, 167.0. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.52; H, 5.92.

3-(2-*tert*-Butoxycarbonylallyl)benzoic Acid Methyl Ester (10). A solution of **7a** (0.30 g, 1.0 mmol) and dimethylmethyleneimmonium iodide (0.49 g, 2.6 mmol) in *tert*-butyl alcohol and THF (1:1 by volume, 8 mL) was stirred at 65 °C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in diethyl ether (15 mL). The organic solution was washed with aq saturated $NaHCO_3$ (15 mL), aq 10% $KHSO_4$ (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated to give 0.23 g of **10** as a colorless oil (81% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.62 (s, 2H), 3.89 (s, 3H), 5.39 (s, 1H), 6.16 (s, 1H), 7.31−7.41 (m, 2H), 7.85−7.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 38.1, 52.0, 80.9, 125.6, 127.5, 128.4, 130.1, 130.2, 133.5, 139.6, 141.2, 165.9, 167.1. Anal. Calcd for $C_{16}H_{20}O_4 \cdot 0.1H_2O$: C, 69.09; H, 7.32. Found: C, 68.98; H, 7.29.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026101S