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A β-AMINO ESTER ENOLATE AS AN ACRYLATE ANION EQUIVALENT

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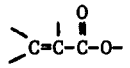
A large number of naturally occurring compounds contain acrylate units and related groups (1). Among these compounds are various α,β-unsaturated carboxylic acids, esters, and lactones. A specific example is ambrosic acid (2), the irritant principle of ragweed pollen.[1] Other examples are compounds 3 and 4 from Ageratina glabrata.[2] Commonly occurring



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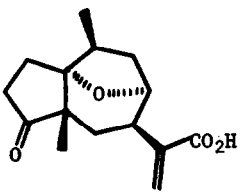

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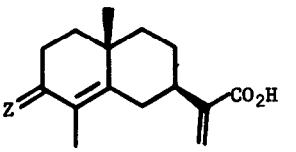
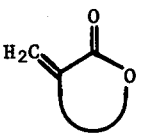


3, Z = H_2

4, Z = O

are various substituted acrylate groups (e.g. tiglates, angelates) as appendages of several physiologically active compounds.[3] Of much current interest are α-methylene lactones (5), many of which are potent antitumor agents[4] and which are actually 2-substituted acrylate derivatives. A number of other important natural products may be considered to be acrylate derivatives in which the carboxy group has been reduced.[5] An example is ambraaldehyde (6).[6] In addition to the importance of acrylates in the field of natural products, acrylates are also valuable synthetic intermediates[7] which undergo quite useful reactions, particularly various Michael-type reactions.



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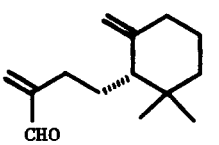

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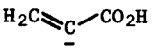
Because of the importance of the acrylates and related compounds, a number of methods have been developed for their synthesis.[8] Two general approaches which have most commonly been employed are (1) α-methylenation of carbonyl compounds[9] and (2) introduction of intact acrylate units.[10] Of these two approaches, the latter appears to be more attractive.

Among these latter methods are the use of synthetic equivalents of the α-carbanion of acrylic acid (7).[7,11] In this communication we are pleased to report a new equivalent of 7 which permits generation of acrylate systems in protected form.



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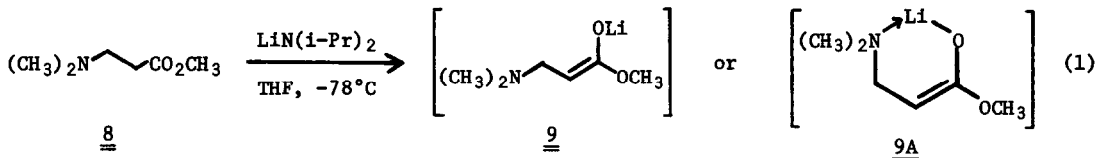
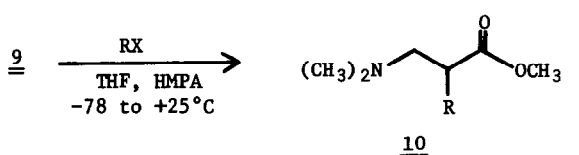
The starting material in our approach is simply methyl 3-(N,N-dimethylamino)propionate (8) which is obtained very easily from methyl acrylate and dimethylamine.[12] Under standard conditions for ester enolate formation,[13] treatment of 8 with lithium N,N-diisopropylamide gives an intermediate (9, equation 1) which appears to be quite stable. Even after prolonged periods of time at room temperature, solutions of 9 undergo subsequent reactions with no significant loss in yields of the resulting products. This stability could possibly be due to the existence of the enolate in a chelated form (9A). The intermediate (9)



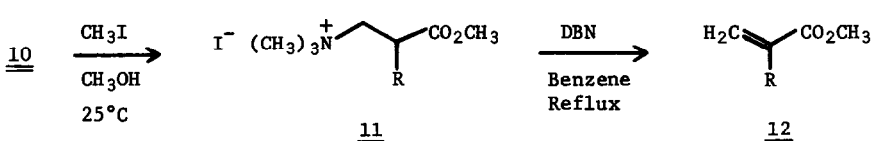
(1)

undergoes reactions with alkyl halides to give the corresponding 2-substituted esters (10, equation 2) which are members of the very useful class of compounds, the Mannich bases.[14] The alkylations proceed efficiently for 1° alkyl iodides and allylic bromides (see Table I) in the presence of hexamethylphosphoric triamide (HMPA), but the enolate (9) is apparently not sufficiently nucleophilic to give good yields of products from other alkyl halides and epoxides.



(2)

The alkylation products (10) may be considered to be masked acrylates. Deprotection entails deamination which is accomplished in two steps. First of all, reaction with methyl iodide[15] to give the quaternary ammonium salts (11) proceeds quantitatively for all cases studied. Subsequent elimination[16] occurs when the salts are treated with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) in benzene at reflux to give the 2-substituted acrylates (12, equation 3). The results of these studies are summarized in Table I.



(3)

Table I. Synthesis of Acrylates

RX	Yields (%):[a] 10	11	12[b]
CH_3I	88	100 [c]	84
CH_3CH_2I	69		
n-C_4H_9I	67, 63 [c]	100 [c]	85, 68 [c]
n-C_4H_9Br	57 [d]		
CH_2=$CHCH_2I$	71, 60 [c]	100 [c]	87
	80, 78 [c]	100 [c]	75

[a]Yields were determined by glpc with an internal standard unless otherwise noted. [b]Overall yield from 10. [c]Isolated yield. [d]Determined by ^{1}H-nmr integration with an internal standard.

A typical procedure follows.

Methyl 2-n-Butylacrylate. To a solution of lithium N,N-diisopropylamide (76 mmol)[13b] in THF (180 ml) at -78°C was added the ester (8, 12.3 ml, 72 mmol). After the solution was stirred at -78°C for 30 min, a solution of n-butyl iodide (8.6 ml, 76 mmol) and HMPA (13.0 ml, 76 mmol) was added. The mixture was stirred at 25°C for 1 hr and quenched by the addition of satd. aq. NH_4Cl (30 ml). The mixture was partitioned between ether and water, and the crude product was isolated from the organic layer. Distillation afforded 8.42 g (63%) of pure 10 (R = n-C_4H_9): bp 50-52°C (0.97 Torr); ir (neat) 1740 cm^{-1}; ^{1}H-nmr ($CDCl_3$) 3.70 (s, 3 H), 2.32-2.78 (m, 3 H), 2.23 (s, 6 H), and 0.6-1.8 (m, 9 H). A portion (2.08 g, 11.1 mmol) of this compound was dissolved in methanol (35 ml), methyl iodide (8.5 ml, 137 mmol) was added, and the solution was allowed to stand at 25°C for 18 hr in the dark. Evaporation of the solvent in vacuo and washing of the resulting solid with ether gave 4.85 g of crude 11 (R = n-C_4H_9). A portion (2.26 g) of this solid was suspended in a solution of DBN (2.0 ml, 16 mmol) and anhyd. benzene (15 ml). After being heated at reflux under nitrogen for 2.3 hr, the mixture was cooled to 25°C and washed with 1 N hydrochloric acid. The product was isolated from the organic layer and purified by distillation to afford 0.496 g (68% overall from 10) of pure 12 (R = n-C_4H_9):[17] bp 85°C (32 Torr); ir (neat) 1722 and 1635 cm^{-1}; nmr ($CDCl_3$) 6.15 (br s, 1 H), 5.53 (m, 1 H), 3.76 (s, 3 H), 2.03-2.53 (m, 2 H), and 0.67-1.60 (m, 7 H).

In summary, we have developed a new, readily available acrylate anion equivalent which permits the convenient synthesis of 2-substituted acrylates, initially in protected form. Work is in progress to increase the nucleophilicity of the enolate (9) to permit reactions with less reactive alkylating agents.

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FOOTNOTES AND REFERENCES

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