Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

The Mannich Reaction of Malonic Acid. An Efficient Route to Some α-Functionalized Acrylates

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Published online: 23 Sep 2006.

SYNTHETIC COMMUNICATIONS, 25(5), 641-650 (1995)

THE MANNICH REACTION OF MALONIC ACID. AN EFFICIENT ROUTE TO SOME α-FUNCTIONALIZED ACRYLATES.

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Abstract: Various α-functionalized acrylates can be easily synthesized by means of the Mannich reaction of malonic acid with paraformaldehyde and secondary aliphatic amines.

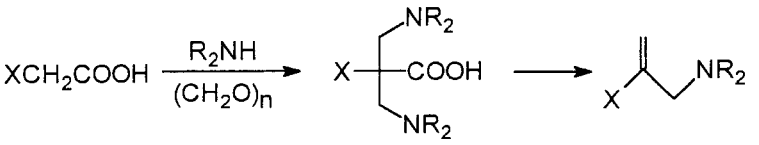
The biological importance and a huge diversity of naturally occuring acrylates eg., α-methylene lactones has made these compounds important synthetic goals and have stimulated the development of new methods and reagents for the preparation of α-functionalized acrylates. Several reports have appeared in the literature that document metodologies used for the construction of α-methylene esters, acids and lactones.[1-7]

The well established strategy for the synthesis of α-substituted acrylates is the Mannich reaction of monosubstituted malonic acids and their esters.[8] In particular, this reaction has successfully been applied to the preparation of α-methylene lactones.[1] In contrast, the Mannich

reaction of acetic acids bearing electron withdrawing substituent has hitherto received little attention (Scheme 1).[9-16]

Our recently published synthesis of 1-(dialkylamino)methylvinylphosphonates[17] was the first example of employing diethylphosphonoacetic acid (**1**, $X = Et_2O_3P$) in the Mannich condensation. An important extension of this method would be the use of malonic acid for the preparation of 2-(dialkylaminomethyl)acrylic acids. Although few representatives of this class of compounds have been described[14-16] general method for their synthesis is still lacking. In this paper we wish to report an efficient and chemoselective transformation of malonic acid (**4**) into 2-(dialkylaminomethyl)acrylic acids **7**, dicycloheksylammonium 2-(alkoxymethyl)acrylates **8** and dicyclohexylammonium 2-(hydroxymethyl)acrylate **9**, respectively (Scheme 2). The latter two conversions demonstrate, that primary alcohol or water can participate in the Mannich type condensations.

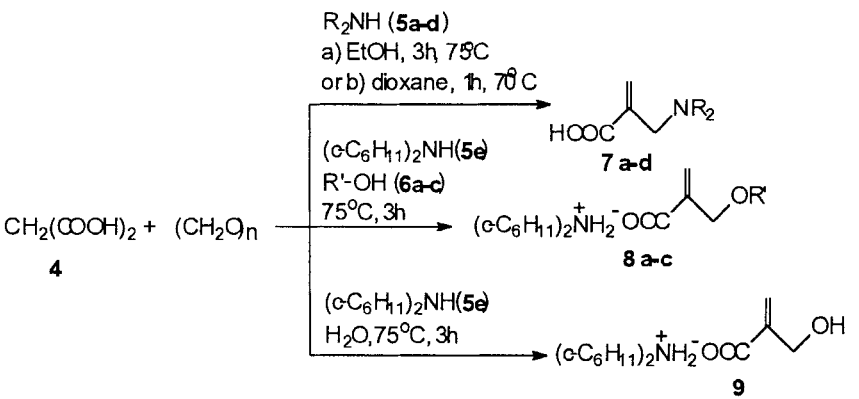
With the aim to prepare amino acids **7a-e** secondary amines **5a-e** were reacted with malonic acid (**4**) and paraformaldehyde (2.2 eq.) in ethanol at 75°C. The obtained results very much depend on the reaction conditions and the used amine (Table). The reactions with the amines **5a-c** afforded the amino acids **7a-c** in good yields. The corresponding reaction with **5d** gave a complex mixture of products in which the amino acid **7d** could not be identified. Surprisingly, under similar conditions, the condensation carried out with dicyclohexylamine (**5e**) proceeded in



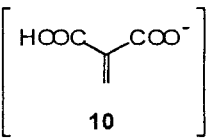
1 **2** **3**

X = EWG

Scheme 1



5,7	R R	6,8	R'
a	$(CH_2)_4$	a	CH_3CH_2
b	$(CH_2)_5$	b	$CH_2{=}CH{-}CH_2$
c	$(CH_2)_2{-}O{-}(CH_2)_2$	c	$CH{\equiv}C{-}CH_2$
d	CH_3CH_2		
e	$c\text{-}C_6H_{11}$		



Scheme 2

Table Preparation of Acrylates **7- 9**

Amine	Solvent	Product[a]	Yield (%)[c]	mp(°C)[d]
5a	EtOH	7a	73	89-90
5a	dioxane	7a	84	
5b	EtOH	7b	75	135-136
5b	dioxane	7b	88	
5c	EtOH	7c	80	106-107
5c	dioxane	7c	92	
5d	EtOH	7d	0	70-71
5d	dioxane	7d	80	
5e	6a	8a	75	87-88
5e	6b	8b	68	96-97
5e	6c	8c	70	116-117
5e	H_2O	9	73	144-145
5e	dioxane	7e + 9[b]	78	

[a] Satisfactory microanalyses obtained

C ± 0.21, H ± 0.16, N ± 0.41

[b] The mixture of **7e** and **9** was not separated. Ratio of **7e:9** = 1:1 established by ^{1}H NMR spectroscopy.

[c] Yields of pure isolated products.

[d] Melting points were not corrected.

totally different manner to yield the ethoxymethylacrylate **8a**. The analogous reactions performed in allyl alcohol (**6b**) and propargyl alcohol (**6c**) afforded the ethers **8b** and **8c**, respectively. Furthermore, it was found that treatment of the acid **4** with paraformaldehyde and the amine **5e** in water at 75°C led to 2-hydroxymethylarylate (**9**).

The above results support the mechanistic pathway involving initial formation of methylene malonate (**10**) as a common intermediate. Nucleophilic addition of the appropriate amine to **10** followed by addition of the resulting enolate to formaldehyde (or to the corresponding Schiff base) and subsequent dexarboxylative elimination results in the formation of the amino acids **7**. In terms of this mechanism it is likely that the reaction with dicyclohexylamine does not occure in a usual way because of steric reasons. However, primary alcohol or water are sufficiently nucleophilic to add to the intermediate **10** producing the acrylates **8** and **9**. The Michael-type reactions with doubly activated methylene compounds have been reported.[18]

In order to gain more insight into chemoselectivity of this process and to search for its optimal conditions the amines **5a-e** were reacted with the acid **4** and paraformaldehyde in dioxane at 70°C. Indeed, under there conditions the amines **5a-c** gave **7a-c** in high yields. The condensation with diethylamine (**5d**) which previously appeared to be a difficult substrate proceeded readily to afford the amino acid **7d** in a good yield. As anticipated, the reaction with dicyclohexylamine produced

the desired amino acid **7e**. However, this product was accompanied by (hydroxymethyl)acrylate **9** resulting from competitive reaction of **10** with water being generated in the course of the whole condensation.

In summary, the Mannich reaction of malonic acid offers a convenient route to chemoselective synthesis of various α-functionalized acrylates. In the light of generally known biological activity of 2-(hydroxymethyl)acrylic acid,[19] its esters[20-21] as well as α-methylene-β-alanine and its derivatives[22-24] the described reaction could be of substantial practical interest.

EXPERIMENTAL

IR spectra were measured using a Specord M 80 (C.Zeiss) instrument. ^{1}H NMR spectra were recorded on a Tesla BS 587 A (80 MHz) spectrophotometer.

2-(Dialkylaminomethyl)acrylic acids 7;

General Procedure:

Method A: To a stirred mixture of malonic acid (10.4 g, 0.1 m) and paraformaldehyde (6.6 g, 0.22 m) in ethanol (150 ml) the appropriate amine was added at room temperature. The suspension was heated at 75°C for 3 h and the resulting solution was evapovaled under reduced pressure. The oily residue thus obtained crystallized on standing. The precipitate was washed with ether, collected by filtration and recrystallized from acetone to give pure product.

Method B: To a stirred mixture of malonic acid (10.4 g, 0.1 m) and paraformaldehyde (6.6 g, 0.22 m) in dioxane (150 ml) the appropriate amine was added at room temperature. The suspension was heated at 70°C for 1 h. The crude product was futher worked up as described above.

Dicyclohexylammonium acrylates 8,9;

General Procedure:

Ta a stirred mixture of malonic acid (10.4 g, 0.1.m) and paraformaldehyde (6.6 g, 0.22 m) in the appropriate solvent (150 ml) (Table) dicyclohexylamine (18.1 g, 0.1 m) was added at room temperature. The suspension was heated at 75°C for 3 h and the resulting solution was evaporated under reduced pressure. The crude product was further worked up as described above. Compound **9** was recrystallized from acetone/chloroform 1:1 mixture.

Spectral data of compounds **7 - 9**.

7a: ^{1}H NMR ($CDCl_3$) δ 1.99-2.16 (m,4H,2xCH_2), 3.15-3.38 (m,4H,2xCH_2), 3.72 (s,2H,NCH_2), 5.49 (d,1H,^2J=1.6, =CH), 6.21 (d,1H,^2J=1.6, =CH), 7.29 (s,1H,COOH); IR (KBr) ν 3416, 1644, 1578, 1452, 1364, 980, 842cm^{-1}.

7b: ^{1}H NMR ($CDCl_3$) δ 1.50-2.0 (m,6H,3xCH_2), 2.6-2.9 (m,4H,2xCH_2), 3.45 (t,2H,^4J=1.1,NCH_2), 5.51 (dt,1H,^2J=^4J=1.1 =CH), 6.31 (brs,1H, =CH), 11.4 (s,1H,COOH); IR (KBr) ν 3420, 1642, 1582, 1452, 1364, 974, 846cm^{-1}.

7c: ^{1}H NMR ($CDCl_3$) δ 2.96 (m,4H,2xCH_2), 3.39 (s,2H,NCH_2), 3.80 (m,4H,2xCH_2), 5.62 (d,1H,^2J = 1.0, =CH), 6.38 (d,1H,^2J = 1.0, =CH), 9.18 (s,1H,COOH); IR (KBr) ν 3432, 1648, 1598, 1458, 1400, 1124, 980, 832cm^{-1}.

7d: ^{1}H NMR ($CDCl_3$) δ 1.28 (t,6H,J = 7.0,2xCH_3), 3.05 (q,4H,J = 7.0,2xCH_2), 3.67 (s,2H,NCH_2), 5.57 (d,1H,^2J = 1.5, =CH), 6.31 (d,1H,^2J = 1.5, =CH), 6.31 (d,1H,^2J = 1.5, =CH), 9.3 (s,1H,COOH); IR (KBr) ν 3408, 1624, 1584, 1478, 1394, 972, 840 cm^{-1}.

7e: ^{1}H NMR ($CDCl_3$) δ 3.63 (br s, 2H,NCH_2), 5.50 (m,1H, =CH), 6.30 (m,1H, =CH). Data taken from the spectrum of the mixture **7e** and **9**.

8a: ^{1}H NMR ($CDCl_3$) δ 1.22 (t,3H,J = 7.1,CH_3), 1.13-1.98 (m,20 H,10xCH_2), 2.95 (m,2H,2CH), 3.56 (q,2H,J = 7.1,CH_2), 4.24 (t,2H,^4J = 1.2,OCH_2), 5.49 (m,1H, =CH), 5.97 (m,1H, =CH), 8.1 (br,2H,NH_2); IR (KBr) ν 2932, 2856, 1612, 1568, 1398, 1112, 922cm^{-1}.

8b: ^{1}H NMR ($CDCl_3$) δ 1.0-2.25 (m,20 H,10xCH_2), 2.70-3.12 (m,2H,2xCH), 4.05 (dt,2H,J = 5.3,^4J = 1.4,OCH_2), 4.25 (t,2H,^4J = 1.6,OCH_2), 5.05-5.40(m,2H, =CH_2), 5.53 (m,1H, =CH), 5.75-6.25 (m,1H, =CH), 6.05 (m,1H, =CH), 8.8 (br,2H,NH_2); IR (KBr) ν 2932, 2856, 1620, 1546, 1398, 1096, 920cm^{-1}.

8c: ^{1}H NMR ($CDCl_3$) δ 1.0-2.25 (m,20 H,10xCH_2), 2.40 (t,1H,^4J = 2.5, ≡CH), 2.75-3.18 (m,2H,2xCH), 4.23 (d,2H,^4J = 2.5,OCH_2), 4.33

(t,2H,^{4}J = 1.7,OCH_2), 5.52 (m,1H, =CH), 6.0 (m,1H, =CH), 8.9 (br,2H,NH_2); IR (KBr) *v* 3116, 2928, 2856, 2104, 1620, 1572, 1388, 1096, 932cm^{-1}.

9: 1.29-2.16 (m,20 H,10xCH_2), 3.0 (m,2H,2xCH), 4.27 (br s,2H,OCH_2), 5.37 (m,1H, =CH), 5.90 (m,1H, =CH), 7.27 (br,3H,NH_2,OH); IR (KBr) *v* 3272, 3040, 2936, 2856, 1608, 1526, 1410, 1064, 934cm^{-1}.

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(Received in the UK 02 August 1994)