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Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

MICHAEL REACTIONS IN AQUEOUS MICELLES OF CETYLTRIMETHYLAMMONIUM BROMIDE

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Published online: 09 Feb 2009.

To cite this article: C. D. Mudaliar, K. R. Nivalkar & S. H. Mashraqui (1997) MICHAEL REACTIONS IN AQUEOUS MICELLES OF CETYLTRIMETHYLAMMONIUM BROMIDE, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 29:5, 584-587, DOI: 10.1080/00304949709355237

To link to this article: http://dx.doi.org/10.1080/00304949709355237

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MICHAEL REACTIONS IN AQUEOUS MICELLES OF CETYLTRIMETHYLAMMONIUM BROMIDE

Submitted by
(08/14/96)

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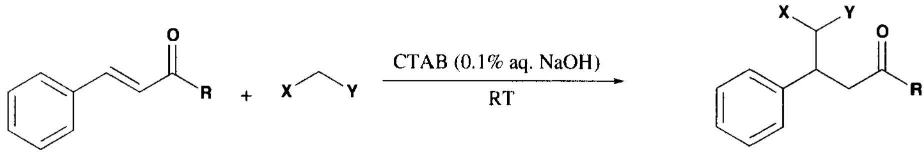
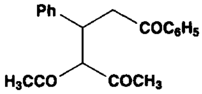
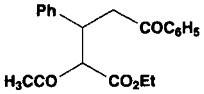
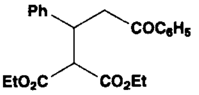
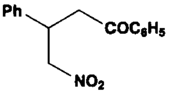
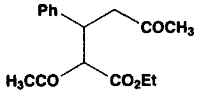
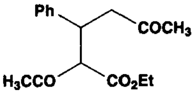
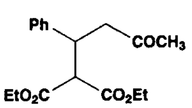
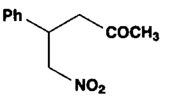
The Michael reaction is widely employed for C-C bond formation.[1] A variety of catalysts ranging from acids, bases, metal complexes, solid supported reagents as well as PTC have been used to promote the process.[2-6] However, choice of the catalyst and its concentration are important factors in determining the success of a reaction.[1a] In recent years, micelles have been extensively used to probe the role of microheterogeneous media in catalysis, reactivity and selectivity of a number of chemical and biochemical processes.[7] However, micellar applications to mediate synthetically useful reactions have been much less explored.[8] We now report the application of aqueous micelles derived from a common surfactant, cetyltrimethylammonium bromide (CTAB) in the catalysis of the Michael reaction.

We chose benzylidene acetophenone (**1**) and benzylidene acetone (**2**) as the Michael acceptors and ethyl acetoacetate, diethyl malonate, acetylacetone and nitromethane as the Michael donors. The reactions were carried out using **1** or **2** (10 mmol) and an appropriate active methylene compound (12 mmol) in 0.1% aqueous NaOH containing CTAB (1×10^{-3} M, 100 mL, pH ca 10.5) according to generalized equation shown below. The mixtures were vigorously stirred at ambient temperature for a period of 8-12 h and the Michael adducts were isolated (*Table*) either directly by filtration (*Entries 1-6*) or by extractive work up (*Entries 7 & 8*). Control experiments established that CTAB micelles significantly accelerate the rate of the reaction (85-95% conversions) compared to their non-micellar counterparts which proceeded only to 5-20% extent for the same reaction times as indicated in the Table. Fair to good yields of the Michael products were obtained in good purity without contamination from side-products.[9] All products have been fully characterized by spectral means and by their mps which are in good agreement with the literature values. It is noteworthy that base labile ethyl acetoacetate and diethyl malonate or the Michael adducts derived therefrom, do not suffer ester hydrolysis under the weakly alkaline conditions employed.



We also successfully realized a one-pot sequential aldol-Michael process as follows. An aldol condensation was first carried out between benzaldehyde and acetophenone (10 mmol each) in the above alkaline CTAB micelles.[10] The reaction mixture was stirred for ca. 7 h whereby the formation of benzylidene acetophenone (**1**) was judged to be complete by TLC. At this point, an equimolar amount of acetylacetone or ethyl acetoacetate was added and the mixture was stirred for an additional 8-10 h. The desired Michael adducts (**3** or **4**) were isolated and crystallized in 60-65% overall yield.

TABLE. Michael Addition in CTAB Micelles[a]

Entry	R	Active methylene compound	Michael Adduct[b]	mp. (°C)	Time (h)	Yield[c] (%)
1	$-C_6H_5$	$CH_3COCH_2COCH_3$	 **3**	145 (lit.[11] 146)	8	77
2	$-C_6H_5$	CH_3COCH_2COOEt	 **4**	120-121 (lit.[11] 121)	9	72
3	$-C_6H_5$	$EtO_2C\,CH_2CO_2Et$	 **5**	65-67 (lit.[11] 67)	12	65
4	$-C_6H_5$	CH_3NO_2	 **6**	100-101 (lit.[11] 101)	8	62
5	$-CH_3$	$CH_3COCH_2COCH_3$	 **7**	92-94 (lit.[12] 94)	10	71
6	$-CH_3$	CH_3COCH_2COOEt	 **8**	128 (lit.[11] 128)	12	65
7	$-CH_3$	$EtO_2CCH_2CO_2Et$	 **9**	oil[d]	10	67
8	$-CH_3$	CH_3NO_2	 **10**	100-101 (lit.[13] 97-98)	12	62

a) All reactions were conducted at room temperature using 12 mmol of active methylene compound and 10 mmol of **1** or **2**. b) Compounds **3-8** precipitated out of the reaction mixture and were crystallized from ethanol. Compound **10** was crystallized from petroleum ether (60-80° fraction). c) Yields refer to TLC homogeneous products. d) ^1H NMR ($CDCl_3$): δ 1.0-1.3 (2t, 6 H); 2.1 (s, 3 H); 2.9-3.0 (m, 2 H); 3.8-4.1 (m, 6 H); 7.15 (s, 5 H_{arom}).[11]

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In conclusion, we have demonstrated the potential utility of aqueous micellar medium in mediating a synthetically useful C-C bond forming process. The reaction conditions are mild, convenient and economical. The yields are high and reactions are free from side-products on account of weakly alkaline conditions.

EXPERIMENTAL SECTION

Mps were determined using apparatus employing electrical heating and are uncorrected. TLC was carried out on precoated silica gel plates (3 x 10 cm). ^{1}H Nmr spectrea were obtained on a Varian RM-390 spectrometer (60 MHz) using TMS as an internal standard.

Typical Procedure for Michael Reaction.- To a 100mL aqueous micellar solution of cetyltrimethylammonium bromide (36.4 mg, 1×10^{-3} M) were added benzylidene acetophenone (2.08g, 10 mmol), and acetylacetone (1.2g, 12 mmol), followed by addition of 1 mL of 10% NaOH solution. The reaction was vigorously stirred at room temperature for 8 h during which time the yellow coloration due to benzylidene acetophenone disappeared along with the precipitation of a copious amount of the colorless Michael adduct **3**. The precipitated adduct was collected and crystallized from ethanol or aqueous ethanol to give colorless crystals (2.37g, 77%) of the adduct mp. 145°, lit.[11] mp. 146°.

Typical Procedure for Sequential Aldol-Michael Process.- Benzaldehyde (1.06g ,10mmol) and acetophenone (1.2g,10mmol) were added to a stirred 100mL solution of cetyltrimethylammonium bromide (36.4 mg, 1×10^{-3} M) followed by addition of 1 mL of 10% NaOH solution. After ca. 7 h , when the formation of benzylidene acetophenone was judged to be complete by TLC, 12 mmol (1.56 g) of ethyl acetoacetate was added to the reaction and the stirring was continued for an additional 9 h. The precipitated Michael adduct was collected, washed with water and crystallized from aqueous ethanol to give compound **4** in 65% yield (2.2 g) mp. 120-121°, lit.[11] mp. 121°.

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9. However, ethyl cyanoacetate failed to react with either benzylidene acetophenone or benzylidene acetone under our standard micellar conditions. To understand this unusual result, we are presently investigating these reactions at higher concentration of alkali and micelles.

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α,β-UNSATURATED SULFONES BY THE WITTIG REACTION OF STABLE YLIDE WITH ALDEHYDES UNDER MICROWAVE IRRADIATION

Submitted by (01/17/96)

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α,β-Unsaturated sulfones are important intermediates in organic synthesis[1] and may be obtained from the condensation of arylsulfonylacetic acid with aldehydes.[2] Kobayashi *et al.* found that tosyl chloride underwent addition with vinylarenes catalyzed by a ruthenium(II) complex; subsequent dehydrochlorination gave the *trans*-α,β-unsaturated sulfones.[3] The reduction of E-β-iodo-α,β-unsaturated sulfones with zinc in acetic acid afforded Z-tosyl-2-arylethenes.[4] α,β-Unsaturated sulfones may also be obtained from the phase-transfer catalyzed condensation of sulfones with aldehydes.[5] Many