New Application of 1,4-Dihydropyridine System: Michael Reactions Mediated by 1,4-Dihydropyridine–Enolate Adduct in Micellar Medium

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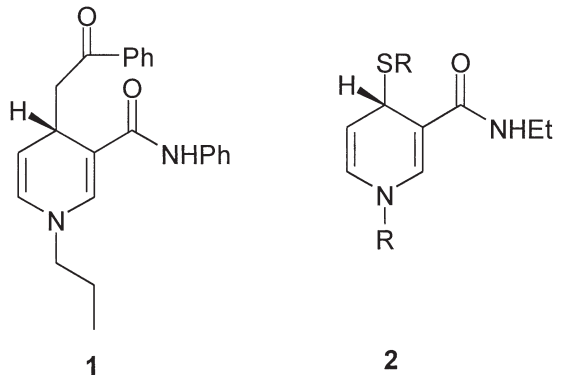
1,4-dihydropyridine-acetophenone enolate adduct, in catalytic amount effects Michael reactions in aqueous cationic micelles of cetyltrimethylammonium bromide. The enolate, generated by dissociation of the adduct abstracts a proton from readily enolizable substrates to bring about the Michael reaction under mild conditions in fair to good yields without side products.

Although, the Michael reaction[1] is one of the oldest C–C bonds forming reactions known, yet it continues to enjoy wide applications in synthetic organic chemistry.[2] A plethora of conditions, and reagents, which include various inorganic and organic bases, acidic and Lewis acid catalysts, metal ion complexes, and solid supported reagents have been employed to effect the Michael additions with varying degree of successes.[3] Several side reactions such as secondary condensation, cyclization, isomerization, rearrangements, and polymerization are known to accompany these conditions, thus necessitating continuing investigation of this versatile reaction.

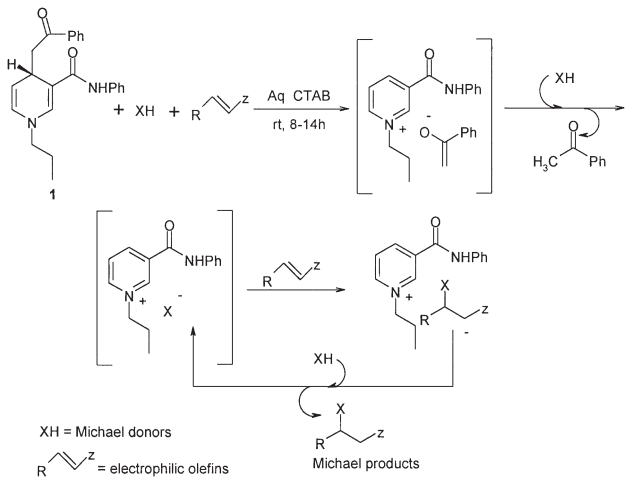
In context to the NAD(P)H mediated enzymatic processes, the redox chemistry of model 1,4-dihydropyridines has been extensively studied.[4] In analogy to the hydride transfer reactions, 1,4-dihydropyridine-enolate adduct **1**[5] and thiolate adduct **2**[6] (Chart 1) have also been shown to transfer enolate and thiolate anions, respectively to electrophilic acceptor substrates under metal ion or Lewis acid catalysis. In the present paper, we wish to report a novel application of adduct **1** in the mediation of Michael reaction under practically neutral conditions.

The mechanistic rationale is based on the premise that the highly basic acetophenone enolate ($pK_a = 24.7$)[7] formed upon ionization of **1** under suitable conditions would be expected to spontaneously remove a proton from relatively more acidic substrates i.e. active methylene compounds ($pK_a \approx 9$–11)[8] to form the corresponding stabilized carbanions. The latter would be captured by the added elctrophilic olefins to form the Michael addition products and a catalytic cycle involving proton exchanges would ensue, as illustrated in the Scheme 1.



1 **2**

Chart 1.



Scheme 1.

To translate the idea of Scheme 1 into practice, we chose an aqueous cationic micelles as the reaction medium on the considerations that, i) a number of dihydropyridinium–anion covalent adducts (cyano, keto, and thiolate adducts) tend to dissociate in aqueous or polar media to form pyridinium ion–anion ion pairs,[9–11] and ii) the aqueous micellar domain would be expected to facilitate dissociation of the adduct **1** by providing the counter anion and, iii) cationic micelles are known to promote nucleophilic processes.[12]

To test the validity these assumptions, as a test case we set up a reaction between a Michael donor, acetyl acetone, and the Michael acceptor, benzylidine acetophenone in the presence of a catalytic amount of **1**[5] (10 mol %), in aqueous solution of a well-known cationic surfactant, cetyltrimethylammonium bromide (1.37×10^{-3} M). The reaction after 8 h of vigorously stirring at room temperature, followed by a simple workup procedure provided to our delight the desired Michael product (Table, Entry 1) in 80% yield. No Michael reaction occurred in the absence of **1** or only in the presence of pyridine as the base.[13] Anionic surfactants, sodium dodecyl sulphate, or neutral surfactants such as Triton X-100 were ineffective in promoting the Michael reaction, whereas the common phase transfer catalyst, tributylammonium bromide (2–5% aq solution) gave a maximum of 20% conversion. These results clearly suggest a unique role of the cationic micelles in promoting both the dissociation of **1** and subsequent proton exchange processes (Scheme 1).

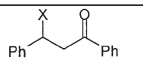
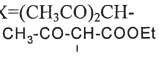
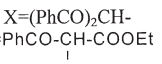
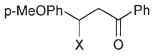
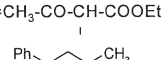
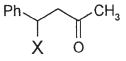
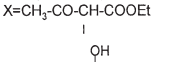
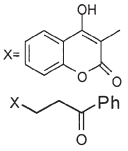
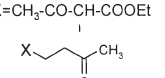
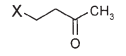
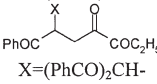
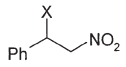
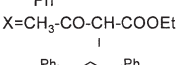
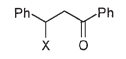
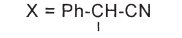
The generality of the process is evident from the examples cited in the Table 1. The reactions are free from side products; only a small amount of acetophenone, generated on proton exchange accompanies the Michael adducts. In general, yields are high and in most cases, the product isolation (except for En-

tries 6, 10, and 11, which require extractive workup) consists of simple filtration and crystallisation. Although, only slightly more acidic than acetophenone, phenylacetonitrile (pK_a = 21.9)[7] also successfully participated, giving a high yield of the Michael product (Entry 14, Table 1). Since, in none of the cases, could we detect the Michael reaction of acetophenone enolate, it is evident that proton exchange with the active methylene substrates must be relatively rapid processes.

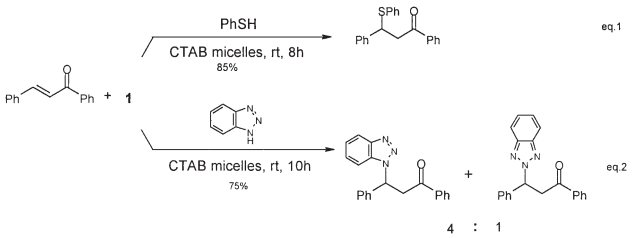
In addition to the C–C bond formation, we could also successfully excute C–S and C–N bond formations. Thus, as representative case, the Michael reaction of benzylidene acetophenone with thiophenol (pK_a = 6.52)[8] and benzotriazole (pK_a = 8.2)[14] was readily accomplished to provide the Michael adducts (Eqs 1 and 2)[16] in high yields in the cationic micellar medium using a catalytic amount of the adduct **1**.

Notable features of the present procedure are the use of cheap, environmentally friendly aqueous medium, milder condition and simple product isolation. Thus, a unique combination of

Table 1. Michael reaction[a] in aq CTAB micelles[15]

Entry	Michael acceptor[a]	Michael[15] product	%Yield / h
			
1	**3**	X=$(CH_3CO)_2CH$-	80(8)
2	**3**		87(12)
3	**3**	X=$(PhCO)_2CH$-	90(10)
4	**3**		90(12)
			
5	**4**	X=$(CH_3CO)_2CH$-	90(12)
6	**4**		67(10)
			
7	**5**	X=$(CH_3CO)_2CH$-	50(14)
8	**5**		60(12)
9	**5**		50(10)
10	**6**		27(12)
			
11	**7**	X=$(PhCO)_2CH$-	25(14)
			
12	**8**	X=$(PhCO)_2CH$-	60(10)
			
13	**9**		43(10)
			
14	**3**		90(12)

[a]Michael acceptor **3-9** are PhCH=CH-COPh, *p*-$MeOC_6H_4CH$=CHCOPh, PhCH=$CHCOCH_3$, PhCOCH=CH_2, CH_3COCH=CH_2, PhCH=CH-CO-$CO_2C_2H_5$ and PhCH=CH-NO_2, respectively.



adduct **1** and cationic CTAB micelles has emerged as a practically non-basic methodology for C–C, C–S, and C–N bond formations.[17] Our work extends the scope of NADH analogues such as the adduct **1** in so far unchartered area of C–C, C–S, and C–N bond formations. Work is currently in progress to use recyclable, immobilized cationic surfactants to enhance the utility of the present procedure.

References and Notes

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