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CLAY CATALYZED SYNTHESIS OF IMINES AND ENAMINES UNDER SOLVENT-FREE CONDITIONS USING MICROWAVE IRRADIATION

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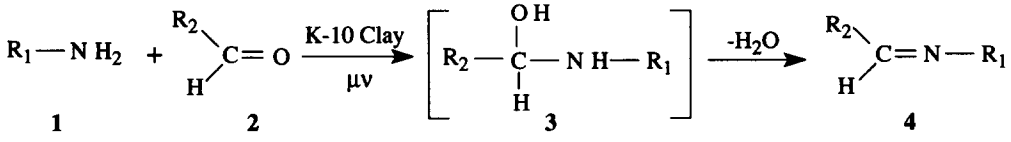
Abstract: *The reactions of primary and secondary amines with aldehydes and ketones, respectively, are accelerated by microwaves under solvent-free conditions in the presence of montmorillonite K 10 clay to afford a high yield synthesis of imines and enamines.* © 1997 Elsevier Science Ltd.

The use of surface active catalysts and inorganic reagents has received much attention in recent years[1,2] because of their enhanced selectivity and milder conditions than those associated with conventional homogeneous reaction procedures. The condensation reaction of aldehydes with primary amines involves addition-elimination steps in which the basic nitrogen of amine **1** adds to the carbonyl carbon of **2**, in the first step; the ensuing intermediate **3**, in the second step, loses a water molecule to generate imine **4** (**Scheme 1**).



1 2 3 4

Scheme 1

Heretofore, the synthesis of imines has been achieved using several reagents such as zinc chloride,[3] titanium(IV) chloride,[4] molecular sieves[5] or alumina.[6] In continuation of our ongoing program to develop environmentally benign synthetic protocols utilizing microwave (MW) irradiation under solvent-free conditions,[7] we wish to report a simple synthetic procedure that is catalyzed by montmorillonite K 10 clay[8,9] for the preparation of imines and enamines. Our approach eliminates the need for the large excess of support usually employed[6] in solid phase reactions and reduces

considerably the longer reaction times and large quantities of aromatic solvents required in the conventional solution phase chemistry that entails the azeotropic removal of water using Dean-Stark apparatus.[8]

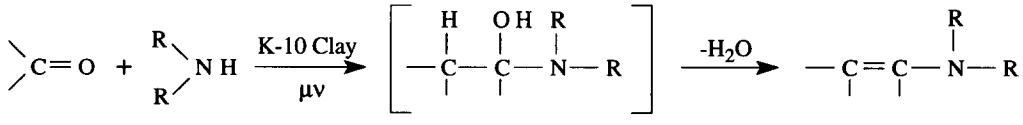
The preparation of benzylidene aniline (**4a**, **Table 1**) is representative of the general procedure employed. To an equimolar (1 mmol) mixture of benzaldehyde (106 mg) and aniline (93 mg) placed in an open glass container, montmorillonite K 10 clay (20 mg) is added and the reaction mixture is irradiated in a microwave oven at full power for 3 minutes. Upon completion of the reaction, as followed by TLC examination, the product is extracted into dichloromethane (3 x 10 ml). Removal of the solvent under reduced pressure affords the benzylidene aniline in 98% yield. Our results for various imines are summarized in **Table 1**.

Table 1: Clay catalyzed synthesis of imines using microwaves[a]

Entry	R_1	R_2	Yield (%)[b]		m. p.	
			found	reported[10]	found	reported[10]
4 a	C_6H_5	C_6H_5	98	90	52	52-3
4 b	C_6H_5	*p*-HOC_6H_4	95	77	195	195
4 c	C_6H_5	*o*-HOC_6H_4	96	81	51.5	52
4 d	C_6H_5	*p*-$Me_2NC_6H_4$	96	88	102	102
4 e	C_6H_5	*p*-$MeOC_6H_4$	97	85	62.5	63

a) The products exhibited physical and spectral characteristics in accord with the assigned structures; b) Isolated and unoptimized yields.

Enamines, an important class of compounds used for selective alkylation and acylation of carbonyl compounds[11] and as valuable intermediates for the synthesis of biologically active natural products,[12] are also prepared by a similar reaction of a secondary amine, **6**, with an aldehyde or ketone, **5**, bearing an α-hydrogen atom (**Scheme 2**). The removal of a water molecule from the intermediate **7** is the driving force for the reaction and is normally achieved by its azeotropic removal,[13a] that is catalyzed by clay[8] or *p*-toluenesulphonic acid.[13b,c]



5 **6** **7** **8**

Scheme 2

Our protocol developed for imines is extendible to the synthesis of enamines with similar efficiency (**Table 2**). The preparation of 1-morpholinocyclohexene, **8a**, is representative of the procedure employed. An equimolar (1 mmol) mixture of cyclohexanone (98 mg) and morpholine (87 mg) is placed in a wide-mouth round bottomed flask to which montmorillonite K 10 clay (20 mg) is added and the mixture is irradiated in a microwave oven at 20% power for 4 min. Addition of morpholine (1 mmol) and further irradiation for 4 min. gives the product which is purified by fractional distillation under reduced pressure to afford 1-morpholinocyclohexene, **8a**, in 97% yield. Our results for a variety of other useful enamines prepared by this method are summarized in **Table 2**.

Table 2: Clay catalyzed synthesis of enamines using microwaves

Entry	Ketone	Amine	Yield (%)[a]		Time	I.R. (film)[b]
			found	rptd.[8]	Min.	$\nu_{C=C}$ [cm^{-1}]
8 a	Cyclohexanone	Morpholine	97	95	8	1646
8 b	Cyclohexanone	Piperidine	95	86	8	1644
8 c	Cyclohexanone	Pyrrolidine	95	95	6	1641
8 d	2-Methylcyclohexanone	Pyrrolidine	75	51	12	1634
8 e	Cyclopentanone	Piperidine	96	93	8	1625

a) Unoptimized yields of oily products that exhibited physical and spectral properties in accord with the assigned structures; b) Perkin-Elmer FT-IR 1600 spectrophotometer.

That the effect is not purely *thermal* [14,15] is obvious from the fact that for similar product yields, longer time periods are needed using alternate heating modes at the same temperature of 110 °C (e.g. oil bath). In separate exploratory experiments, the clay catalyzed preparation of imines could be accomplished using ultrasonic irradiation for 30 minutes, but these reactions fail to undergo completion in the case of enamines even after several hours. Clearly, the use of a microwave oven is convenient and cleaner when compared to other experimental conditions because it eliminates the use of excessive aromatic solvents and Dean-Stark apparatus for azeotropic removal of water, and proceeds efficiently in a shorter period of time. MW heating has been used for a wide variety of applications including the rapid synthesis of organic compounds.[15-18] The useful solution phase chemistry utilizing microwaves[16] is finding practical applications under solvent-free 'dry' conditions.[7,17-18] This is an approach that is environmentally benign in view of the reduction in the use of solvents which are normally employed in large amounts.

In conclusion, we have developed a simple procedure for the synthesis of imines and enamines that proceeds rapidly under solvent-free conditions, provides better

product yields, and does not require azeotropic water elimination using large excess of aromatic solvents.[8,13] The further elaboration of *in situ* generated enamines into useful products in one-pot procedures using microwave irradiation is currently being investigated.

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