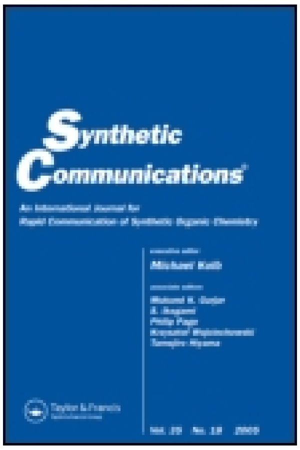

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A Convenient and Effective Method for Synthesizing β-Amino-α,β-Unsaturated Esters and Ketones

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A Convenient and Effective Method for Synthesizing β-Amino-α,β-Unsaturated Esters and Ketones

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ABSTRACT

A convenient and effective method for the preparation of β-amino-α,β-unsaturated esters and ketones has been developed through silica gel-catalyzed and solvent-free reactions of β-dicarbonylic compounds with ammonia and primary amines.

Key Words: Amination; β-Diketone; β-Keto ester; β-Amino-α,β-unsaturated ketone; β-amino-α,β-unsaturated ester; Silica gel.

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INTRODUCTION

β-Amino-α,β-unsaturated esters and ketones are useful synthetic intermediates,[1] particularly in the construction of heterocyclic compounds such as dihydropyridines,[2–5] pyridines,[6,7] pyrimidines,[8] indoles,[9] and isothiazoles.[10] Recently β-amino-α,β-unsaturated acids have also been widely used in synthesis of β-amino acids and peptidyl mimetics.[11–13]

Several methods for the preparation of β-amino-α,β-unsaturated esters and ketones have been developed. The generally employed method for their preparation entails the reaction between β-dicarbonylic compounds and amines in benzene with azeotropic removal of water.[14,15] However, there are problems associated with the use of low boiling amines as starting materials.[16] It is necessary either to pass a rapid stream of gaseous amine through the refluxing diketone solution,[17] or to operate a reaction in an autoclave at 130–150°C.[18,19] Moreover, the first procedure requires a large excess of amine. For the latter methods, the reaction cannot be easily monitored, the yields are not quantitative, and polymerization occurs.[16] Some successful modifications have been reported, such as the use of ammonium or alkylammonium acetate,[20] Lewis acids such as boron trifluoride etherate,[17] alumina (neutral) or montmorillonite K-10 as solid catalysts in benzene[21,22] or as solid supports.[23,24] Other methods such as addition of an amine to a β-halovinyl ketone[25] or ester,[26] hydrogenation (Raney-Ni) of isoxazoles,[27] palladium catalyzed amination of electron-deficient olefins,[28] palladium induced dehydrogenation of a β-amino ketone,[29] are also described in the literature. Herein we describe an effective and convenient method for preparation of β-amino-α,β-unsaturated esters and ketones in very high yield through silica gel-catalyzed and solvent-free reactions of β-dicarbonylic compounds with ammonia and primary amines.

RESULTS AND DISCUSSION

As part of our program directed towards the synthesis of pharmaceutically active dihydropyridine derivatives, we had to synthesize β-amino-α,β-unsaturated esters and ketones as starting materials. Reviewing literature examples, a convenient and solvent-free method for the preparation using montmorillonite K-10 as solid support has been reported.[23,24] In this method amines can be applied in aqueous solution and the use of solvents for removal of water is avoided. Due to the unavailability of montmorillonite K-10 in our hands we rationalized that silica gel having weak acidity would be suitable replacement as solid support for the reaction. Firstly, we found that an almost quantitative yield was obtained in reactions of acetoacetone and ethyl

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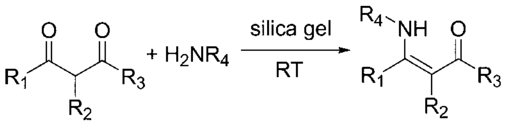

1 **2** **3**

Scheme 1. Synthesis of β-amino-α,β-unsaturated ketones and esters.

acetoacetate with ammonia by using silica gel. After extensive optimization we found that the same results were obtained by using a catalytic amount of silica gel as catalyst. In this work we describe a convenient and effective method for the preparation of a series of β-amino-α,β-unsaturated esters and ketones in very high yields through silica gel-catalyzed and solvent-free reactions of ammonia, primary amines and β-keto esters including a β-keto lactone, acetoacetone (Sch. 1). The results are summarized in the Table 1. Anilines worked very well, but required relative long reaction time.

In this method, amines can be used either as such or in aqueous solution. In case of liquid products, after filtration and evaporation, almost pure compounds (>98% purities) were obtained in nearly quantitative yield. Pure products can be obtained by chromatographic separation on silica gel for low yielding products. Solid products were obtained through extraction by washing with dichloromethane and crystallization or flash column chromatography on silica gel. As can be seen for products **3e**, **3j**, **3o** and **3t**, the reaction also leads to good yields for amines with a bulky group (MeCHPh). The advantages of the procedure reported here are: (i) high yields; (ii) high purity of the desired products; and (iii) easy workup.

All known products were characterized and their spectroscopic data are in agreement with those reported in the literature.[24,30–38]

CONCLUSION

In summary, a convenient, effective and environment-friendly method for preparation of β-amino-α,β-unsaturated esters and ketones has been developed through silica gel-catalyzed and solvent-free reactions of β-dicarbonylic compounds with ammonia and primary amines.

EXPERIMENTAL

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector

Table 1. Synthesis of β-amino-α,β-unsaturated ketones and esters.

Product	R^1	R^2	R^3	R^4	Reaction time	Yield (%)	Mp (°C)
3a	Me	H	Me	H	24 hr	99	30–32 (33–35)[24]
3b	Me	H	Me	Me	3 hr	99	31–33 (37–39)[24]
3c	Me	H	Me	Bn	30 min	92	Oil (Oil)[24]
3d	Me	H	Me	Ph	35 hr	95	48–49 (49–50)[24]
3e	Me	H	Me	$PhCHCH_3$	2 hr	99	71–72.5 (70–71)[30]
3f	Me	H	OEt	H	4 hr	99	Oil (Oil)[24]
3g	Me	H	OEt	Me	8 hr	99	Oil (Oil)[24]
3h	Me	H	OEt	Bn	30 min	99	Oil (Oil)[24]
3i	Me	H	OEt	Ph	24 hr	86	Oil (Oil)[24]
3j	Me	H	OEt	$PhCHCH_3$	2 hr	99	Oil (Oil)[31]
3k	$-(CH_2)_3-$		OEt	H	10 min	99	36–37 (55–57)[32]
3l	$-(CH_2)_3-$		OEt	Me	10 min	99	44–45 (45–46)[33]
3m	$-(CH_2)_3-$		OEt	Bn	10 min	99	62–63 (26–27)[34]
3n	$-(CH_2)_3-$		OEt	Ph	24 hr	99	Oil (Oil)[35]
3o	$-(CH_2)_3-$		OEt	$PhCHCH_3$	30 min	99	Oil (Oil)[36]
3p	Me	$-(CH_2)_2O-$		H	5 hr	99	74–76
3q	Me	$-(CH_2)_2O-$		Me	4 hr	99	107–108 (96–98)[37]
3r	Me	$-(CH_2)_2O-$		Bn	2 hr	99	119–120 (100.9–101.4)[38]
3s	Me	$-(CH_2)_2O-$		Ph	48 hr	78	94–95 (74.7–77.4)[38]
3t	Me	$-(CH_2)_2O-$		$PhCHCH_3$	3.5 hr	99	67–68 (78–79)[38]

22 FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (300 MHz) spectrometer in $CDCl_3$ solution with TMS as an internal standard and chemical shifts are reported in ppm. Mass spectra were obtained on a VG-ZAB-HS spectrometer. CH analyses were performed on an Elementar Vario EL analyzer.

Synthesis of β-Amino-α,β-Unsaturated Esters and Ketones; General Procedure

Amine **2** (12 mmol, pure amine, or ammonia or amine in an aqueous solution) was added dropwise to the suspension of silica gel (100 mg, 10 mg for diketone, Qingdao Ocean Chemical Industrial Co.) in the dicarbonylic compound **1** (10 mmol) and the resulting mixture was stirred at room temperature for 10 min–24 hr (monitored by TLC). For liquid products, crude products were obtained after removal of silica gel by filtration. Pure liquid products were obtained by purification on a silica gel column. For solid products, crude products were obtained after extraction with dichloromethane and removal of solvent. The purification was performed by column chromatography on silica gel using hexane/acetone as eluent.

2-(1-Aminoethylidene)butyrolactone (3p)

Colorless crystal. Mp 74–76°C. IR (KBr): 1685 (C═O), 3324 and 3423 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.93$ (s, 3H, CH_3), 2.82 (t, $J = 7.6$ Hz, 2H, CH_2), 4.29 (t, $J = 7.6$ Hz, 2H, CH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 20.41$, 25.76, 65.10, 87.02, 154.45, 172.93. MS (EI): $m/z = 127$ (M^+, 83), 98 (M^+-HCO, 20), 83 (M^+-CO_2, 11), 69 (M^+-CO_2CH_2, 100). Calcd for $C_6H_9NO_2$ (127.14) C: 56.68; H: 7.13; N: 11.02. Found: C: 56.51; H: 7.33; N: 11.12.

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