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An Efficient Chemo- and Stereoselective Synthesis of Enaminones and Enaminoesters Using (Bromodimethyl)sulfonium Bromide Under Solvent-Free Conditions

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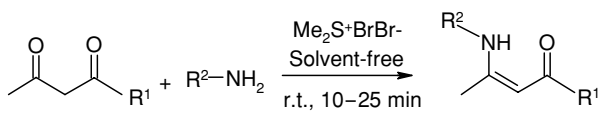
ABSTRACT: *(Bromodimethyl)sulfonium bromide has efficiently been employed for chemo- and stereoselective conversions of β-dicarbonyl compounds into β-enaminones and β-enaminoesters by a treatment with amines at room temperature under solvent-free conditions.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:630–633, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20477

INTRODUCTION

β-Enaminones and β-enaminoesters are valuable intermediates for the synthesis of different bioactive molecules [1] including antibacterial, antitumor, and anticonvulsant agents [2]. They are also used for the preparation of amino acids [3], aminols [4,5], peptides [6], and alkaloids [7]. β-Enaminones can be prepared by condensation of β-dicarbonyl compounds with amines under reflux in an aromatic solvent with azeotropic removal of water [8]. Recently, some other methods applying SiO_2/microwaves [9], $SiO_2/HClO_4$ [10], Al_2O_3 [11], montmorillonite K-10 [12], $Bi(TFA)_3$ [13], $Bi(TFA)_3$-TBAB [14], $NaAuClO_4$ [15], $Zn(ClO_4)_2 \cdot 6H_2O$ [16], $CeCl_3 \cdot 7H_2O$ [17], $InBr_3$ [18], and CAN [19] have been developed. However, many of these methods have many disadvantages such as high temperatures, long reaction times, low yields, strongly acidic conditions, and use of costly reagents and hazardous solvents. Thus, an improved method for the preparation of β-enaminones and β-enaminoesters is essential.

RESULTS AND DISCUSSION

As a part of our work [20] on the development of useful synthetic methodologies, we have discovered that β-enaminones and β-enaminoesters can efficiently be synthesized from β-dicarbonyl compounds by treatment with amines in the presence of (bromodimethyl)sulfonium bromide (Scheme 1).



1 **2** **3**

SCHEME 1

This article is Part 156 in the series "Studies on novel synthetic methodologies."

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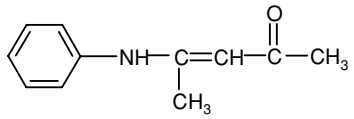
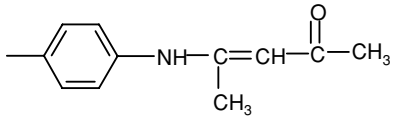
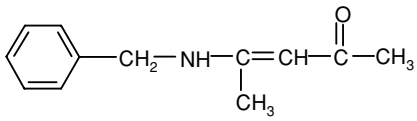
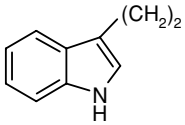
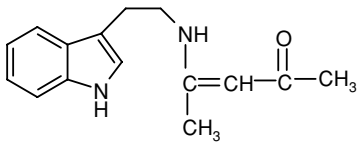
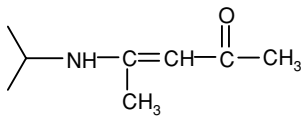
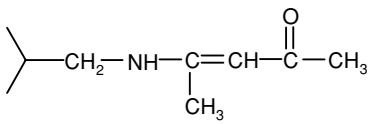
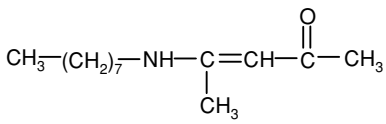
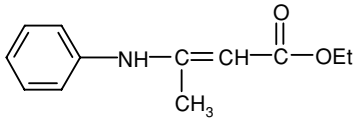
A series of β-enaminones and β-enaminoesters were prepared from different β-dicarbonyls (β-diketones and β-ketoesters) and amines (aromatic and aliphatic) under solvent-free conditions. The products were formed in excellent yields within a short period of time (10–25 min). Considering yields and reaction times (bromodimethyl)sulfonium bromide was found to be more efficient than several other reagents that are previously used.

In the present method, an amine attacks only a ketone carbonyl of a diketone or a ketoester. Thus, the other carbonyl group will always be free. The products (Table 1) were found to possess (*Z*)-selectivity secured by an intramolecular hydrogen bonding. This was evidenced from their ^{1}H NMR spectra that showed the appearance of the proton of the —NH group in the range of δ 8.5–12.5.

(Bromodimethyl)sulfonium bromide [21] works under mild reaction conditions. Previously, it was utilized to carry out some synthetic transformations but its catalytic activity was not fully explored. In the present case, it has been efficiently employed for the preparation of enamine derivatives.

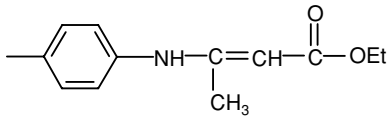
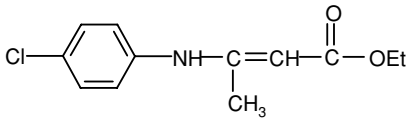
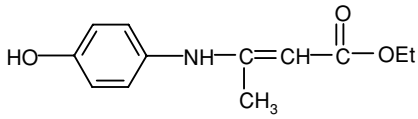
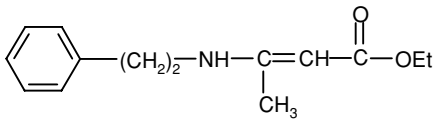
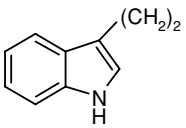
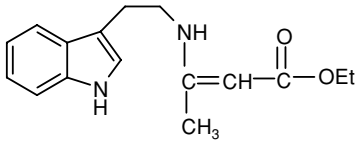
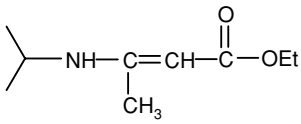
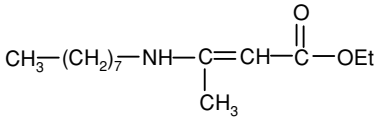
In conclusion, we have described a simple and efficient method for the synthesis of β-enaminones and β-enaminoesters by the treatment of β-dicarbonyl compounds with amines, using (bromodimethyl)sulfonium bromide as a catalyst. The mildness of the conversion, solvent-free conditions, short reaction times, and high yields are the notable

TABLE 1 Synthesis of β-Enaminones and β-Enamino Esters Using (Bromodimethyl)Sulfonium Bromide Under Solvent-Free Conditions[a]

Entry	*R^1*	*R^2*	*Time (min)*	*Product*	*Isolated Yield (%)*
a	Me	Ph	20		93
b	Me	*p*-Me-Ph	18		91
c	Me	Ph-CH_2	23		93
d	Me		24		91
e	Me	$(CH_3)_2CH$	17		89
f	Me	$(CH_3)_2CH$-CH_2	18		93
g	Me	CH_3-$(CH_2)_7$	20		92
h	OEt	Ph	15		94

(*Continued*)

TABLE 1 Continued

Entry	*R^1*	*R^2*	*Time (min)*	*Product*	*Isolated Yield (%)*
i	OEt	*o*-Me-Ph	15		93
j	OEt	*p*-Cl-Ph	20		91
k	OEt	*p*-OH-Ph	17		90
l	OEt	Ph-$(CH_2)_2$	15		87
m	OEt		20		93
n	OEt	$(CH_3)_2CH$	16		89
o	OEt	CH_3-$(CH_2)_7$	15		88

[a]The structures of the products were determined from spectral (^{1}H NMR and MS) data.

advantages of the present method. An important utility of (bromodimethyl)sulfonium bromide is also disclosed.

EXPERIMENTAL

General Experimental Procedure

To a mixture of a dicarbonyl compound (1 mmol) and an amine (1.2 mmol), (bromodimethyl) sulfonium bromide (10 mol%) was added. The mixture was stirred at room temperature, and the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The extract was concentrated, and the gummy residue was subjected to column chromatography [silica gel: hexane-EtOAc (4:1)] to obtain pure β-enaminone or β-enaminoester.

The spectral (^{1}H NMR and MS) data of some representative products are given below:

3b: ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.20 (1H, br s), 7.11 (2H, d, $J = 7.8$ Hz), 6.97 (2H, d, $J = 7.8$ Hz), 5.12 (1H, s), 2.35 (3H, s), 2.09 (3H, s), 1.94 (3H, s); EIMS: m/z 189 [$M^{+\cdot}$].

3d: ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.87 (1H, br s), 9.19 (1H, s), 7.92 (1H, dd, $J = 8.0$, 1.5 Hz), 7.28 (1H, dd, $J = 8.0$, 1.5 Hz), 7.18–6.98 (3H, m), 4.85 (1H, s), 3.50–3.22 (2H, m), 3.03–2.96 (2H, m), 1.96 (3H, s), 1.83 (3H, s); FABMS: m/z 265 [M + Na]$^+$.

3e: ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.80 (1H, br s), 4.87 (1H, s), 3.72 (1H, m), 1.96 (3H, s), 1.94 (3H, s), 1.26 (6H, d, $J = 7.0$ Hz); EIMS: m/z 141 [$M^{+\cdot}$].

3i: ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.29 (1H, br s), 7.08 (2H, d, $J = 8.0$ Hz), 6.95 (2H, d, $J = 8.0$ Hz), 4.60 (1H, s), 4.11 (2H, q, $J = 7.0$ Hz), 2.35 (3H, s), 1.96 (3H, s), 1.24 (3H, t, $J = 7.0$ Hz); FABMS: m/z 242 [M + Na]$^+$.

3m: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.60 (1H, br t, $J = 8.0$ Hz), 8.41 (1H, br s), 7.45 (1H, d, $J = 8.0$ Hz), 7.22–6.99 (3H, m), 6.89 (1H, br s), 4.38 (1H, s), 4.05 (2H, q, $J = 7.0$ Hz), 3.50–3.38 (2H, m), 2.98–2.89 (2H, m), 1.80 (3H, s), 1.24 (3H, t, $J = 7.0$ Hz); FABMS: m/z 273 $[M + H]^+$.

3n: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.50 (1H, br s), 4.31 (1H, s), 4.02 (2H, q, $J = 7.0$ Hz), 3.66 (1H, m), 1.92 (3H, s), 1.25 (3H, t, $J = 7.0$ Hz), 1.22 (6H, d, $J = 7.0$ Hz); EIMS: m/z 171 $[M^{+\cdot}]$.

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