

Tetrabutylammonium Bromide (TBAB)-Catalyzed Rapid Conversion of β -ketoesters into β -Enaminoesters under Solvent-free Conditions

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ABSTRACT

When used with a mortar and pestle at 25 °C in a solvent-free environment, tetrabutylammonium bromide (TBAB) is characterized as an effective catalytic system for the synthesis of β -enaminoesters from β -ketoesters. This method has a number of benefits, including shorter reaction times, use of inexpensive and readily available catalyst, compatible reaction conditions, and high product yields.

KEYWORDS

amines, β -enaminoesters, β -ketoesters, tetrabutylammonium bromide and catalysis

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INTRODUCTION

β -Enamino esters are versatile intermediates for the synthesis of nitrogen containing compounds.^{1–4} Also, they are important subunits present in some biologically important natural products as well as therapeutic agents.^{5,6} Due to the importance of β -enamino ester derivatives as bioactive leads and versatile building blocks, their synthesis and applications have long been an active topic in organic synthesis.

The synthesis of β -enaminoesters has been described using a variety of methodologies, including tosyl imines, imidoyl halides, addition of enamines or ketimines to activated carboxylic acid derivatives, addition of an ester or amide enolate to a nitrile, and others.^{7–22} These compounds can also be successfully produced by direct condensation of β -ketoesters with amines.^{23;24;25} The majority of the protocols are well documented, although they have limitations in chemical yields, harsh reaction conditions, and a lack of widespread applicability. Thus, there is a great need to design a better catalyst for the synthesis of β -enaminoesters.

Synthetic chemists continue to research novel synthetic methods employing new reagents and catalysts to perform chemical transformations. Due to their low production costs and simplicity of usage, solvent-free based synthetic methodologies have found increasing use in the manufacture of pharmacologically relevant heterocyclic compounds.^{26–30} On the other hand, the mechanochemical method has been increasingly popular due to its affordability and low impact on the environment. Mechanical grinding is one of the typical methods used in solvent-free reactions. Because of its ease of use, clean reaction profile, and potential for larger-scale application with the right experimental set-up, mechanical grinding has emerged as a powerful tool in the paradigm of synthetic organic chemistry.^{31;32}

Tetrabutylammonium bromide (TBAB) is inexpensive, but it's also more selective, non-corrosive, easy to recycle, and is operationally simple. It has been found to be efficient in a number of organic transformations.^{33;34;35} Only a small amount of TBAB is required to catalyze several reactions such as esterification, oxidation, reduction, and alkylation. Furthermore, it functions as an effective co-catalyst for a range of coupling reactions. It has also been effectively used in a range of molten organic processes as a zwitterionic solvent.

In this article, we present a mild and useful protocol for the synthesis of β -enaminoesters from β -ketoesters from the reaction of

amine, β -ketoester in the presence of tetrabutylammonium bromide (10 mol%) in solvent-free conditions at ambient temperature.

EXPERIMENTAL

In CDCl₃ at 300 MHz, the ¹H NMR spectra were captured using TMS as the internal standard. For solid materials, KBr pellets were used to record IR spectra, and neat was used for liquid samples. Using silica gel, column chromatography was carried out (100–200 mesh). In relation to internal TMS, chemical changes are expressed in ppm, while J values are reported in Hz.

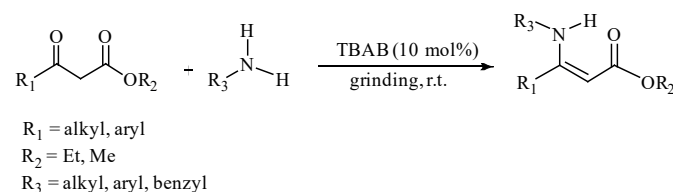
GENERAL PROCEDURE

A mortar and pestle was used to grind the amine (1.5 mmol), β -ketoester (1 mmol), and a tetrabutylammonium bromide (TBAB) (10 mol%) for the allotted amount of time. Water was added once the reaction was completed (TLC), and diethyl ether was used to extract the result. Under low pressure, the organic layer was dried (with Na₂SO₄) and concentrated. By using column chromatography (silica gel 100–120 mesh, petroleum ether: ethyl acetate = 9:1), the crude product was refined to afford the corresponding β -enaminoester (all known compounds).

RESULTS AND DISCUSSION

A systematic study was first conducted to assess the effectiveness of tetrabutylammonium bromide as a catalyst for the reaction of aniline and ethylacetoacetate under diverse circumstances (Scheme 1).

After 20 hours, the reaction between ethyl acetoacetate and aniline produced a meagre amount of product in the absence of a catalyst (entry 1, Table 1), and the outcomes were poor in the presence of solvents (entries 2–5, Table 1). The reaction was completed in 10 minutes with only 10 mol% of tetrabutylammonium bromide, and a nearly quantitative yield of the corresponding β -enaminoester (95%)



Scheme 1. Synthesis of β -enaminoesters

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Table 1: Reaction between aniline and ethyl acetoacetate under various conditions.

Entry	Solvent	Catalyst (mol%)	Time (min; [h])	Yield (%)
1	neat	–	[20]	15
2	CH ₂ Cl ₂	2.0	45	65
3	THF	2.0	60	70
4	CH ₃ CN	2.0	45	60
5	CHCl ₃	2.0	45	65
6	neat	2.5	[1]	50
7	neat	5.0	[1]	65
8	neat	7.5	[1]	85
9	neat	10.0	10	95
10	neat	12.0	10	95
11	neat	15.0	10	95

was obtained. We then optimized the quantity of TBAB for this reaction at ambient temperature and without a solvent (entries 6–11, Table 1). It's important to notice that increasing the amount of TBAB had no effect on yield or response time (entries 10–11). The reaction was not completed with less than 10 mol% tetrabutylammonium bromide, even after milling the reaction mixture for an hour. This resulted in a low yield of the product (50–85%).

The results displayed in Table 2 proved that the approach worked for primary, benzylic, and aromatic amines. For instance, the conversion of methyl and ethyl acetoacetates into the corresponding β -enaminoesters was simple. Excellent yields and short reaction times are just two of the many noteworthy advantages the current approach has over those that have been described. A study claims that this reaction finds steric hindrance when β -ketoesters contain a bulky amine or have a substituent other than hydrogen in the α -position, requiring lengthy reaction times and severe reaction conditions. High product yields were reached even with cyclic and aromatic β -ketoesters (entries, j, k, and l, Table 2).

Table 2: Synthesis of β -enaminoesters from β -ketoesters and Amines. ^aYields of pure isolated products

Entry	Amine	Ketoester R = CH ₃ /C ₂ H ₅	Product	Time (min)	Yield ^a (%)
a				10	88
a'				10	90
b				10	87
b'				10	88
c				10	95
c'				10	92
d				15	93
d'				15	91
e				50	90
e'				52	89
f				60	89
f'				62	91
g				30	90
g'				30	87
h				45	88
h'				40	82
i				50	78
i'				50	81
j				15	75
k				12	68
l	n-BuNH ₂			15	72

CONCLUSION

As a result, we have developed a novel methodology for the synthesis of β -enaminoesters in conditions devoid of solvent. The key appealing aspects of this method include the use of a cheap and widely accessible catalyst (TBAB), experimental simplicity, a straightforward work-up procedure, and a quick response.

SUPPLEMENTARY MATERIAL

Supporting information is available for this article online.

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