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An Efficient Synthesis of β-Enaminoketone/Ester Under Grinding Condition Using Calcium Bromide as Solid Support Catalyst

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ABSTRACT

Calcium bromide was used as a catalyst in the synthesis of β-enaminoketone/ester from 1,3-dicarbonyl compound and amines. The reaction was carried out in mortar and pestle at room temperature. The process is mild, efficient, eco-friendly and cost-effective with the use of very small amount of catalyst; avoiding use solvent, simple product separation, and high yield. We compare this grinding reaction condition with reaction in solvent and we got better results with the grinding reaction condition.

Keywords: Calcium bromide, β-Enaminoketone, Solvent free, Grindstone Chemistry, Green synthesis

INTRODUCTION

Solid-state chemistry has been developed rapidly as a competent and selective method, since molecules in the crystals have been arranged tightly and regularly. One of the methods belonging to this etiquette is a simple grinding method called a grindstone (mechanochemical) method which reactants are ground simply by mortar and pestle. Grinding is attracting many organic chemists due to it is performed in the absence of solvent, leading to safe and environmentally friendly synthesis. In addition to this, the proposed technique does not require external heating, leading to energy efficient synthesis and may be regarded as more cost-effective and ecologically favourable procedure in chemistry. Mechanical-induced breaking of molecular bonds, reduction of particle size, increase in surface area, formation of defects and local melting occur due to the kinetic energy supplied during grinding in solvent-free organic reactions based on grinding. The conveyance of very low measures of energy through friction in this operation leads to more efficient mixing and close contact between the starting materials on a molecular scale [1].

β-enaminones and β-enamino esters have been widely used as crucial intermediates in organic synthesis due to its variable nature as electrophiles and nucleophiles [2]. Enaminones are widely used as versatile building blocks for synthesis of important bioactive heterocyclic compounds and different biological active compounds [3]. Due to the broad range of pharmaceutical activity and key intermediate in organic synthesis create great interest of organic chemist to synthesize this molecule. The well-known route for the synthesis of β-enamino ketones and esters involves the direct condensation of β-dicarbonyl compounds with amines under reflux in an aromatic solvent with azeotropic removal of water [4]. A variety of catalysts such as metal salts [5-8], metal triflate [9-12], solid supported reagent [13-16], metal oxide [17,18], $Bi(TFA)_3$ [8], β-cyclodextrin in water [19], $VO(acac)_2$ [20], Ceric ammonium nitrate [21], $[(PPh_3)AuCl]/AgOTf$ [22], Ionic liquid promoted [23], $Zn(ClO_4)_2.6H_2O$ [24], trimethylsilyl trifluoromethane sulphonate (TMSTf) [25], Tris(Hydrogensulfato)Boron or trichloroacetic acid [26], Microwave assisted [27], Microwave radiation/K-10 [28], Phosphomolybdic acid (PMA) [29], K-10/Ultrasound [30], formic acid [31].

However, some of these methods have synthetic shortcomings such as use of expensive or combinations of catalysts, use of toxic solvent, longer reaction times, use of excess amount of catalyst, low yield, tedious work-up procedures, lack of selectivity, in some cases catalyst preparation requires, use of toxic metal catalysts. Therefore, there is scope to develop a new and efficient method for synthesis of β-enamination of 1,3-dicarbonyl compounds.

Calcium bromide is obtained by the interaction of bromine and milk of the lime in the presence of ammonia. It is readily soluble in water and absolute ethanol [32]. It is thermally and chemically stable. Use of calcium bromide in organic synthesis is very rare [33,34]. Herein, we report the use of calcium bromide as a catalyst for the synthesis of β-enaminoketone/ester under solvent free condition.

EXPERIMENTAL SECTION

General

All chemicals were purchased from Loba chemicals, Merck, Sigma Aldrich and used without further purification. Commercially available Calcium bromide is used as a catalyst and it is purchased from Loba chemicals. Melting points were determined by open capillary method and are uncorrected. All products are known and their structure is confirmed by Infra-red (IR), Proton Nuclear Magnetic Resonance (^{1}HNMR), Carbon-13 Nuclear Magnetic Resonance (^{13}CNMR), High Resolution Mass Spectrometry (HRMS) and comparison of this spectral data with those reported in the literature. Progress of the reaction was monitored by Thin Layer Chromatography (TLC) on precoated silica gel 60 F_{254} sheets.

General experimental procedures for synthesis of β-enaminones

Method A: In a mortar and pestle, equimolar amounts of primary amines (1 mmol) and β-dicarbonyl compound (1 mmol) along with calcium bromide (2 mol%, 0.02 mmol, and 0.0047 g) as a catalyst were placed. The reaction mixture was continuously grinded for the specified time as given in Tables 1 and 2. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water and product was extracted with ethyl acetate (2 × 15 ml) and washed with water and brine solution. The combined organic phases were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using ethyl acetate-petroleum ether (2:8 v/v). All products are known and their structure is confirmed by IR, ^{1}HNMR, ^{13}CNMR and HRMS.

Table 1: Synthesis of β-enaminoketones and β-enamino esters using calcium bromide under solvent free grinding condition[a]

Entry	β-dicarbonyl compounds	Amines	Product (3)	Time (min)		(%) Yield[b]		M.P. [Ref]
				Under grinding	In solvent	Under grinding	In solvent	
1	Acetylacetone	Aniline	3a	25	120	97	89	45-47 [17]
2	Acetylacetone	4-methylaniline	3b	22	90	92	83	66-68 [16]
3	Acetylacetone	4-chloroaniline	3c	27	85	90	81	61-62 [16]
4	Acetylacetone	4-nitro aniline	3d	55	300	87	78	141-143 [17]
5	Acetylacetone	4-methoxyaniline	3e	30	74	94	83	45-46 [16]
6	Acetylacetone	o-nitroaniline	3f	120	360	No reaction	No reaction	-
7	Acetylacetone	2-methyl aniline	3g	65	240	74	57	38-40 [4]
8	Acetylacetone	2-methoxyaniline	3h	75	280	58	47	Oil [18]
9	Acetylacetone	methyl amine	3i	20	82	84	74	46-48 [23]
10	Acetylacetone	butyl amine	3j	25	78	87	78	Oil [16]
11	Ethyl acetoacetate	Aniline	3k	30	105	92	82	Oil [16]
12	Ethyl acetoacetate	4-methyl aniline	3l	24	94	88	81	Oil [16]
13	Ethyl acetoacetate	4-methoxy aniline	3m	20	68	90	80	47-48 [16]
14	Ethyl acetoacetate	4-chloro aniline	3n	38	130	83	73	56-58 [16]
15	Ethyl acetoacetate	4-bromo aniline	3o	45	170	81	72	53-56 [18]
16	Ethyl acetoacetate	1-naphthylamine	3p	55	200	74	61	Oil [18]
17	Ethyl acetoacetate	benzyl amine	3q	50	240	78	70	Oil [26]
18	Ethyl acetoacetate	2-methyl aniline	3r	67	265	58	50	Oil [4]
19	Ethyl acetoacetate	butyl amine	3s	30	110	73	59	Oil [22]
20	Ethyl acetoacetate	2-nitro aniline	3t	120	360	No reaction	No reaction	-
21	1-phenylbutane-1,3-dione	Aniline	3u	75	210	78	71	107-109 [31]
22	1-phenylbutane-1,3-dione	4-methoxy aniline	3v	50	240	81	74	92-95 [31]
23	1-phenylbutane-1,3-dione	4-methyl aniline	3w	54	200	85	77	86-87 [31]
24	1-phenylbutane-1,3-dione	4-chloroaniline	3x	63	260	82	74	127-129 [31]

a: Reaction conditions: Method A in mortar and pestle and Method B with stirring in Ethanol amine (1 mmol) and β-dicarbonyl compound (1 mmol) and calcium bromide (2 mol %, 0.0 2 mmol) were placed b: isolated yield

Method B: To a mixture of β-dicarbonyl compound (1 mmol) and primary amines (1 mmol) in ethanol (5 ml), calcium bromide (2 mol%, 0.02 mmol, 0.0047 g) was added at room temperature with stirring. The reaction mixture was stirred for the specified time as given in Tables 1 and 2. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with water and product was extracted with ethyl acetate (2 × 15 ml) and washed with water and brine solution. The combined organic phases were dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using ethyl acetate-petroleum ether (2:8 v/v).

Table 2: Synthesis of cyclic β-enaminoes using calcium bromide under solvent free grinding condition[a]

Entry	β-dicarbonyl compounds	Amines	Product (4)	Time (Min)		% Yield[b]		M. P.[Ref]
				Under grinding	In solvent	Under grinding	In solvent	
1	Dimedone	aniline	4a	45	125	92	86	185-186 [16]
2	Dimedone	4-chloroaniline	4b	53	160	86	80	192-194 [26]
3	Dimedone	4-bromoaniline	4c	60	194	82	79	220-221 [16]
4	Dimedone	4-methoxy aniline	4d	40	135	91	85	193-195 [16]
5	Dimedone	4-nitroaniline	4e	75	250	78	70	192-193 [26]
6	Dimedone	2-methoxy aniline	4f	85	300	63	57	125-127 [16]
7	Dimedone	3-nitro aniline	4g	70	256	82	76	168-170 [26]
8	Dimedone	2-nitroaniline	4h	120	360	No reaction	No reaction	-
9	Dimedone	benzyl amine	4i	65	175	77	73	127-128 [16]
10	Dimedone	butyl amine	4j	65	182	86	79	117-119 [16]

a: Reaction conditions: Method A in mortar and pestle and Method B with stirring in Ethanol amine(1 mmol) and β-dicarbonyl compound (1 mmol) and calcium bromide (2 mol%, 0.02 mmol) were placed b: isolated yield

RESULTS AND DISCUSSION

The condensation of aniline and acetyl acetone was selected as a model reaction. Initially we have various metal salts such as calcium chloride, ferric sulphate, magnesium bromide, magnesium chloride, calcium bromide, calcium carbonate, calcium nitrate, magnesium nitrate, magnesium sulphate, as catalyst for the condensation reaction under solvent free grinding condition and results are summarized in table (Table 3). The model reaction is performed using 1 mmol of aniline, 1 mmol of acetyl acetone and 0.2 mmol of catalyst in mortar and pestle. From Table 3 it was observed that calcium bromide was found an efficient catalyst for synthesis of β-enaminoketone/ester with 97% yield. Calcium sulphate, magnesium sulphate, calcium carbonate, ferric sulphate did not give the desire product.

Table 3: Screening of catalyst for condensation reaction between acetyl acetone and aniline under solvent free grinding condition[a]

S. No.	Catalyst	Product	Time (min)	% Yield[b]
1	$CaCl_2$	3a	75	83
2	$MgCl_2$	3a	90	85
3	$SrCl_2$	3a	135	76
4	$BaCl_2$	3a	140	72
5	$CaBr_2.2H_2O$	3a	25	97
6	$MgBr_2$	3a	40	91
7	$Ca(NO_3)_2$	3a	55	75
8	$Mg(NO_3)_2$	3a	74	72
9	$CaSO_4.2H_2O$	3a	180	No reaction
10	$MgSO_4$	3a	180	No reaction
11	$CaCO_3$	3a	180	No reaction
12	$Fe_2(SO_4)_3$	3a	180	No reaction

a: Reaction conditions are: 1 mmol of aniline, 1 mmol of acetyl acetone and 0.2 mmol of catalyst under solvent free grinding condition; b: isolated yield after purification

Similarly, aniline (1 mmol) and acetylacetone (1 mmol) were selected as the model substrates to optimise the amount of calcium bromide. The catalyst loading was optimized by increasing the amount of calcium bromide from 0.5-20 mol% for 1 mmol scale reaction. The yield increased with the increase in catalyst amount (Table 4, entries 1-5). Nevertheless, there was a very minor increase in the yield when the catalyst loading has increased from 2-20 mol%. From table it was observed that 2 mol% of the catalyst was sufficient to obtain the best yield. Although reaction has also well proceeded with 0.5 mol% and 1 mol% of catalyst, but to achieve good yields, long reaction times were usually required to achieve yields comparable with those obtained with 2 mol% of catalyst (Table 4, entries 1-2).

Table 4: Optimising amount of catalysts for synthesis of β-enaminoketone[a]

Entry	Catalyst/Mol%	Time (Min)	% yield[b]
1	0.5	65	74
2	1	52	83
3	2	25	97
4	5	20	97
5	10	20	95
6	15	20	96
7	20	20	94

a: Acetyl acetone (1 mmol) and aniline (1mmol) were used b: Isolated yield after purification

To study generality and scope of our methodology, the reaction was examined with calcium bromide (2 mol %) under solvent free grinding condition at room temperature. First we studied the scope of the reaction with various substituted aromatic and aliphatic primary amines with acetyl acetone and ethyl acetoacetate as shown in Figure 1. The results are displayed in Table 1. Table 1 showed that the reactions proceeded smoothly and with high yields were obtained. It was also observed that aromatic amines with electron donating substitutents or halogen substituents required a shorter reaction time than aromatic amines with electron-withdrawing groups. Additionally, the reaction with aliphatic amines proceeded readily requiring a shorter time than that required for the reaction with aromatic amines.

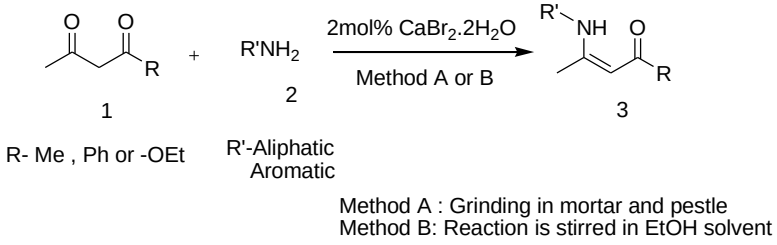
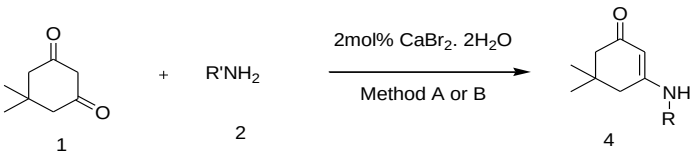


Figure 1: Synthesis of β-enaminoketones and β-enamino esters using calcium bromide under different condition

Also, this method was extended for preparation of cyclic β-enaminoketones under the same reactions conditions. The cyclic β-diketone reacted with various substituted primary aromatic amines as shown in Figure 2. Similarly aromatic amines with electron-donating substituents also required a shorter reaction time than aromatic amines with electron-withdrawing groups.



Method A : Grinding in mortar and pestle
Method B: Reaction is stirred in EtOH solvent

Figure 2: Synthesis of cyclic β-enamioes and β-enamino esters using calcium bromide under different condition

Consequently, it was found that all amines reacted only at the methyl ketone carbonyl for β-dicarbonyl compounds and β-ketoester. Also, β-dicarbonyl compounds and β-ketoester gave (*Z*)-β-enamino ketones and esters whereas the cyclic diketones give solely (*E*)-β-enamino ketones. The *Z*-form configuration of the products was confirmed by ^{1}HNMR analysis. The proton of the-NH group appearing in a lower field ($\delta > 8.0$) indicated formation of the intramolecular hydrogen bond which stabilized the products.

In summary, we have developed a simple, efficient and environmentally benign method for synthesizing β-enamino ketones and esters using a neutral and readily available catalyst calcium bromide under solvent free condition using grinding technique. The advantages of this method is high yield, easily available, non-toxic and inexpensive catalyst, short reaction time, low amount of catalyst is required to carry out the reaction, applicable to wide variety of substrates, avoiding use of solvent and finally conformity with green chemistry principles Table 5.

Table 5: Comparison of the result of synthesis of β-enaminoketones in presence of different catalysts

Entry	Catalyst	Catalyst loading	Conditions	Time (min)	(%) Yield	Ref
1	$InBr_3$	0.05 mmol	Solvent free, R.T.	50	98	[4]
2	$CoCl_2.6H_2O$	0.25 mmol, 0.0058 g	R.T.	50	95	[5]
3	$Bi(TFA)_3$	0.05	R.T./H_2O	5-180	63-98	[8]
4	$Er(OTf)_3$	1 mol%	CH_2Cl_2/R.T.	120-360	71	[10]
5	P_2O_5/SiO_2	30% w/w	Solvent free 80°C	120	Good to excellent	[13]
6	CAN	20 mol%	CH_3CN/R. T.		72-93	[21]
7	[(PPh_3)AuCl]/ AgOTf	0.03 mmol/ 0.03	Solvent free, R.T.	2- 5	70-98	[22]
8	Silica sulfuric acid	0.4 g	Solvent free 80°C	10	89	[16]
9	Tris(Hydrogensulfato)Boron	10%	120°C	7-10	75-85	[26]
10	$CaBr_2.2H_2O$	2 mol% 0.0047 g	R.T.	25-120	97	In this paper
11	B_2O_3/Al_2O_3	15 mmol **(0.03 g)**	Solvent free, R.T.	60	95	[18]
12	Silica supported $Fe(HSO_4)_3$	0.25 mmol, 0.22 g	Solvent free, R.T.	7-40	60-95	[15]
13	Phosphomolybdic acid	1 mol%	CH_3CN/R.T.	1-3 h	Good to excellent	[29]

REFERENCES

[1] J. Safari, S. Gandomi-Ravandi, RSC adv., **2014**, 11486-11492.
[2] A. Elassar, A. El-Khair, *Tetrahedron*., **2003**, 59, 8463-8480.
[3] B. Govindh, B. Diwakar, Y.L.N. Murthy, *Org. Commun.*, **2012**, 5, 105-119.
[4] Z. Zhang, L. Yin, Y. Wang, *Adv. Syn. Catal*., **2006**, 348, 184-190.
[5] Z. Zang, J. Hu, *J. Brazil Chem. Soc*., **2006**, 17, 1447-1451.
[6] J. Lin, L.F. Zhang, *Monatsh. Chem.*, **2007**, 138, 77-81.
[7] Z.H. Zhang, Z.C. Ma, L.P. Mo, *Indian J. Chem.*, **2007**, 46, 535-539.
[8] A. Khosropour, M. Khoadaei, M. Kookhazadeh, *Tetrahedr. Lett.*, **2004**, 45, 1725-1728.
[9] J. Yadav, V. Kumar, R. Rao, A. Priyadarshini, P. Rao, B.V.S. Reddy, K. Nagaiah, *J. Mol. Catal. A. Chem.*, **2006**, 256, 234-237.
[10] R. Dalpozzo, A. Nino, M. Nardi, B. Russo, A. Procopio, *Synthesis*., **2006**, 7, 1127-1132.
[11] F. Epifano, S. Genovese, M. Curini, *Tetrahedr. Lett*., **2007**, 48, 2717-2720.
[12] C. Feng, N. Chu, S. Zhang, J. Cai, J. Chen, H. Hu, M. Ji, *Chemical Papers*., **2014**, 68, 1097-1103.
[13] M. Mohammadizadeh, A. Hasaninejad, M. Bahramzadeh, Z.S. Khanjarlou, *Syn. Commun*., **2009**, 39, 1152-1165.
[14] J. Sun, Z. Dong, P. Li, F. Zhang, S. Wei, Z. Shi, R. Li, *Mater. Chem. Phy*., **2013**, 140, 1-6.
[15] H. Eshghi, S. Seyedi, E. Safaei, M. Vakili, A. Farhadipour, M. Bayat-Mokhtari, *J. Mol. Catal A: Chem*., **2012**, 363-364, 430-436.
[16] A. HasanineJad, A. Zare, M. Mohammadizadeh, M. Shekouhy, A. Moosavi-Zare, *E. J. Cem.*, **2010**, 7, 1546-1554.
[17] S. Shendage, J. Nagarkar, *Curr. Chem. Lett.*, **2013**, 2, 145-152.
[18] J. Chen, C. Zhang, W. Gao, H. Jin, J. Ding, H. Wu, *J. Brazil Chem. Soc.*, **2010**, 21, 1552-1556**.**
[19] M. Khodaei, A. Khosropour, C. Cardel, *J. Chin Chem. Soc*., **2008**, 55, 217-221.
[20] R. Laskar, N. Begum, M. Mir, S. Alis, A. Khan, *Tetrahedr. Lett.*, **2013**, 54, 436-440**.**
[21] M. Paira, R. Misra, S.C. Roy, *Indian J. Chem.*, **2008**, 47, 966-969.
[22] M. Zhang, A. Abdukader, Y. Fu, C. Zhu, *Molecules.*, **2012**, 17, 2812.
[23] A. Singh, N. Gupta, M. Sharma, J. Singh, *Indian J. Chem.*, **2014**, 53, 900-906.
[24] G. Bartoli, M. Bosco, M. Locatelli, E. Marcantoni, P. Melchiorre, L. Sambri, *Syn. Lett.*, **2004**, 239-242.
[25] C. Cartaya-Marin, D. Henderson, R. Soeder, A. Zapata, *Syn. Commun.*, **1997**, 27, 4275-4283.
[26] Z. Karimi-Jaberi, Z. Takmilifard, *Eur. Chem. Bull.*, **2013**, 2, 211-213.
[27] D. Sharma, Bandna, C. Reddy, S. BalKumar, A.K. Shil, N.R. Guha, P. Das, *RSC. Adv.*, **2013**, 10335-10340.
[28] H.T.S. Braibante, M.E.F. Braibante, G.B. Rosso, D.A. Oriques, *J. Brazil Chem. Soc*., **2003**, 14, 994-997.
[29] K. Nagaiah, K.V. Purnima, D. Sreenu, S. Jhansi, R.S. Rao, J.S. Yadav, *Syn. Commun*., **2012**, 42, 461-468.

[30] C.J. Valduga, A. Squizani, H.S. Braibante, E.F. Braibante Mara, *Synthesis.*, **1998**, 1019-1022.
[31] S.A. Patil, P.A. Medina, D. Gonzalez-Flores, J.K. Vohs, S. Dever, L.W. Pineda, M.L. Montero, B.D. Fahlman, *Syn. Commun.*, **2013**, 43, 2349-2364.
[32] http://encyclopedia2.thefreedictionary.com/Calcium+Bromide
[33] W. Han, H. Yu, E. Kennedy, J. Mackie, B. Dlugogorski, *Environ. Sci. Technol*., **2008**, 42, 5795-5799.
[34] P. Kulkarni, *Journal Marocain de Chimie Hétérocyclique*., **2016**, 15, 71-78.