Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Efficient synthesis of symmetrical bisamides catalyzed by reusable hydroxyapatite

Gurusamy Ramachandran, Ramachandran Saraswathi, Mayilvasagam Kumarraja, Palsamy Govindaraj & Thirumeni Subramanian

To cite this article: Gurusamy Ramachandran, Ramachandran Saraswathi, Mayilvasagam Kumarraja, Palsamy Govindaraj & Thirumeni Subramanian (2018) Efficient synthesis of symmetrical bisamides catalyzed by reusable hydroxyapatite, Synthetic Communications, 48:2, 216-222, DOI: 10.1080/00397911.2017.1395888

To link to this article: https://doi.org/10.1080/00397911.2017.1395888

SYNTHETIC COMMUNICATIONS®
2018, VOL. 48, NO. 2, 216–222
https://doi.org/10.1080/00397911.2017.1395888

Taylor & Francis
Taylor & Francis Group

Efficient synthesis of symmetrical bisamides catalyzed by reusable hydroxyapatite

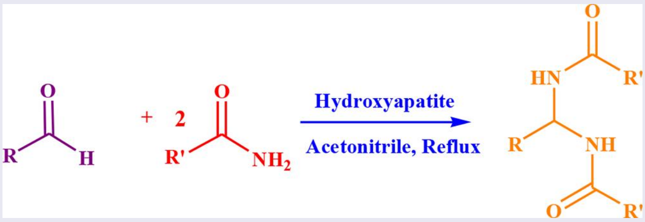
Gurusamy Ramachandran[a], Ramachandran Saraswathi[a], Mayilvasagam Kumarraja[b], Palsamy Govindaraj[a], and Thirumeni Subramanian[a]

[a]Department of Chemistry, Saiva Bhanu Kshatriya College, Aruppukottai, India; [b]Centre for Research and Post-Graduate Studies in Chemistry, Ayya Nadar Janaki Ammal College (autonomous), Sivakasi, Tamilnadu, India

ABSTRACT

Efficient synthesis of symmetrical bisamides is achieved by hydroxyapatite catalyst. Hydroxyapatite catalyzes the reaction between aldehydes and amides to afford bisamides at reflux conditions in 87–95% yields in acetonitrile medium. The catalyst is readily recovered and reused at least three times without loss in its catalytic activity. This method is noteworthy that, symmetrical bisamides are synthesized by fast, simple, effective, and environmentally benign heterogeneous protocol.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 31 May 2017

KEYWORDS
Aldehydes; amides; hydroxyapatite; reusability; symmetrical bisamides

Introduction

The importance of diamides in chemistry and biology is well recognized and that play a major role in the development and composition of biological and pharmacological systems. In particular, symmetrical and unsymmetrical *N,N′*-alkylidene bisamides and their derivatives are found as key structural subunits for the construction of peptidomimetic frameworks. One of the challenges facing chemists is to develop novel transformations that are not only efficient, selective and high yielding but are also environmentally benign.[1,2] Organic transformations and preparation of industrial products are profound transformation which accommodates sustainability criteria, invention of new methods with green chemistry principles.[3] Use of hazardous and homogeneous catalysts is generally connected with problems in separation, recovery and regeneration of the catalysts which can be minimized using heterogeneously catalyzed reaction,[4] which includes easy separation from reaction mixtures by simple filtration or centrifugation, safe disposal,

CONTACT Thirumeni Subramanian chemsubbu84@gmail.com Department of Chemistry, Saiva Bhanu Kshatriya College, Aruppukottai-626101, Virudhunagar (Dist.), Tamil Nadu, India.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article can be accessed on the publisher's website.

low cost, tolerance to a wide range of temperatures and pressures, long lifetime, eco-friendly nature and regenerability.[5] The catalysts must be pure, mixed with other catalysts or dispersed on an inert support, e.g., hydroxyapatite, layered double hydroxide (LDHs), zeolites, and clays.[6,7]

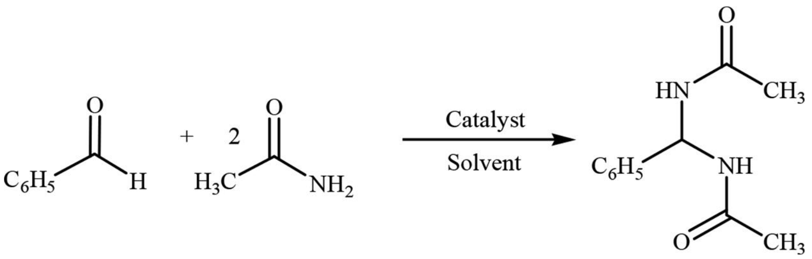
Hydroxyapatite, $Ca_5(PO_4)_3(OH)$ (HAP), is the integral part of bone and numerous reports available as bioceramics and catalysts.[8,9,10] Hydroxyapatite catalyst easily available in nature like accessory minerals in igneous rocks, small quantities in most metamorphic rocks and the mineral of teeth also in bone is an impure form of hydroxyapatite.[11,12] Hydroxyapatite possess a number of interesting properties such as adsorption and thermal stability, ion-exchange character, acid-base properties, and interesting important properties of synthetic hydroxyapatite is its ability to undergo substitution of both cations (Ca^{2+}) and anions (PO_4^{3-} and/or OH^-) by the ion exchange. This ion exchange of Ca^{2+} by either bivalent or trivalent ions can be expected to influence the biological, chemical and physical properties of hydroxyapatite. Hydroxyapatite has also been used as novel support for many organic transformations such as Suzuki–Miyaura and Heck type cross-coupling,[13] oxidation of primary amines,[14] chalcone derivatives,[15] aldol condensation,[16] 5-Substituted 1*H*-Tetrazoles,[17] Sonogashira reaction,[18] epoxidation of styrene,[19] Coupling of diiodoalkenes,[20] selective hydrogenation of nitroarenes[21] which must be attributed to hydroxyapatite cation-exchanged ability.

The amides are highly useful and valuable compounds that have numerous biological applications.[22,23] Among the amides, the *N,N′*-alkylidene bisamides are helps to construction of peptide frameworks,[24,25] HIV inhibitors, calcium channel blockers, α-adrenergic and neuropeptide Y antagonists, antihypertensive, antitumor, antibacterial and anti-inflammatory agent.[26] Bulky bisamides are served as lubricants in polymer applications, powder coatings, defoamers and flow modifiers in asphalt applications. Symmetrical alkylidene bisamides are synthesized by the direct reaction of aldehydes and amides with various catalysts such as *p*-TSA,[27] boric acid,[28] phosphotungtic acid,[29] triflic acid[30] and silica supported polyphosphoric acid (SiO_2-PPA)[31] although the results were not satisfying, long reaction time, harsh reaction conditions, unsatisfactory yields and use of large quantity of catalyst. Therefore, improvements with respect to the above have been continuously sought. In recent years, many reports focus on the catalytic properties of hydroxyapatite. Our careful literature survey at this stage revealed that there is no report on the use of hydroxyapatite catalyst for the synthesis of symmetrical bisamides. As part of our continuing interest in developing efficient and environmental benign synthetic methodologies,[32–35] herein we report a convenient and efficient method for the synthesis of symmetrical bisamides by condensing aryl aldehydes and amides using hydroxyapatite as a reusable and heterogeneous catalyst.

Results and discussion

Typical reaction parameters including several catalysts, solvents, time and temperature are screened in preliminary studies. Acetamide and benzaldehyde are chosen as the model substrate to optimize the reaction conditions. Without any catalyst, this reaction did not take place in ethanol solvent at room temperature and even at 80°C (Table 1, entries 1 and 2). Next, the above test reaction is investigated in the presence of various catalysts such as $FeCl_3$, $ZnCl_2$, and $CuNO_3$ separately in refluxing acetonitrile (Table 1, entries 3–5), all

Table 1. Effect of catalyst on model reaction for synthesis of symmetrical bisamides.[a]



Entry	Catalyst	Solvents	Time (h)	Temp (°C)	Yield (%)[b]
1	None	None	24	Rt	None
2	None	Ethanol	24	80	None
3	$FeCl_3.3H_2O$	Acetonitrile	3	reflux	55
4	$ZnCl_2$	Acetonitrile	3	reflux	58
5	$CuNO_3$	Acetonitrile	3	reflux	62
6	Calcium nitrate	Ethanol	10	80	42
7	Diammonium hydrogen phosphate	Ethanol	10	Rt	38
8	Ammonium hydroxide	Ethanol	10	Rt	40
9	Hydroxyapatite	None	10	Rt	22
10	Hydroxyapatite	Acetonitrile	3	80	95

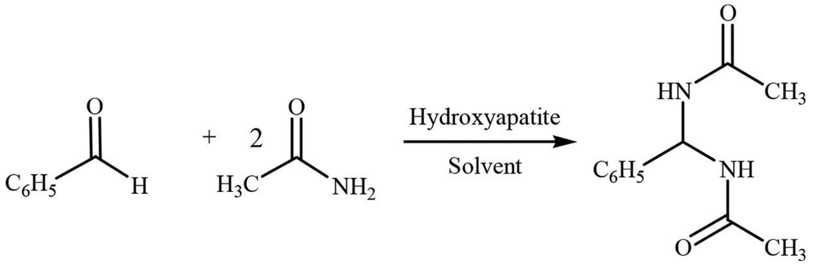
[a] Reaction conditions: Benzaldehyde (1 mmol), acetamide (2 mmol), solvent (2 ml), catalyst (50 mg).
[b] Isolated yields.

the catalysts did catalyze the reaction, albeit in low efficiency. We then turned our attention toward sources of hydroxyapatite such as diammonium hydrogen phosphate, ammonium hydroxide, calcium nitrate and only moderate yields are observed (Table 1, entries 6,7 and 8; yields 42, 38, 40 correspondingly), which might indicates that these should be interaction form with active sites PO_4^{3-} of hydroxyapatite to form product. Lowering the temperature (Rt) became detrimental to the reaction (Table 1, entry 9), while increasing the temperature (80 °C) has significant effect on the reaction (Table 1, entry 10). The result demonstrated that 80 °C is found to be the optimum temperature. Better catalytic performance is observed in hydroxyapatite with 95% yield in acetonitrile medium at 80 °C. Higher catalytic activity may be attributed to the higher surface property of hydroxyapatite catalyst.

Our next attempts are focused on the evaluation of the efficiency of various solvents. The reaction did not take place in the absence of solvent (Table 2, entry 1). Significant amount of symmetrical bisamide is detected when the reaction performed in chloroform (Table 2, entry 2). Moderate yields are observed when the reaction proceeded in acetone, methanol, etc (Table 2, entries 3–10). Optimizations revealed that the acetonitrile solvent can accelerate the reaction, enabling the completion at 80 °C within 3 h to produce a 95% yield (Table 2, entry 11).

These interesting preliminary results promoted us to expand the scope of hydroxyapatite catalyst with a wide range of substrate combinations and the results are summarized in Table 3. It is found that there is no remarkable electron and position effects from the aromatic aldehydes for this reaction, as evidenced by benzaldehydes with either an *p*-nitro, *p*-Cl, and *o*-hydroxy substituent, also achieved greater yields with aldehydes bearing electron-withdrawing groups. In addition, our catalytic system efficiently reacts with benzamides too and affords the corresponding bisamide derivatives in excellent yields (Table 3, entries 2, 4, 6, 8, 10, and 12). Notably, sterically demanding *ortho*-substituents did not dampen the reaction

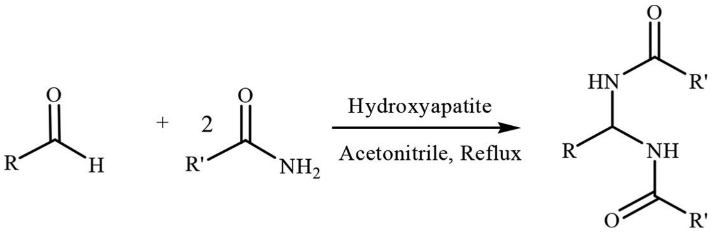
Table 2. Screening impact of solvents on the reaction between benzaldehyde and acetamide catalyzed by hydroxyapatite.[a]



Entry	Solvents	Time (h)	Temp (°C)	Yield (%)
1	None	10	80	None
2	Chloroform	8	50	68
3	Dichloromethane	8	50	55
4	Toluene	8	80	35
5	Methanol	3	80	70
6	Ethanol	3	80	72
7	Ethylacetate	5	50	45
8	1,4-dioxane	8	60	60
9	Dimethyl sulfoxide	5	100	74
10	Dimethyl formamide	5	100	70
11	Acetonitrile	3	reflux	95

[a] Reaction conditions: Benzaldehyde (1 mmol), acetamide (2 mmol), solvent (2 mL), catalyst 50 mg.
[b] Isolated yields.

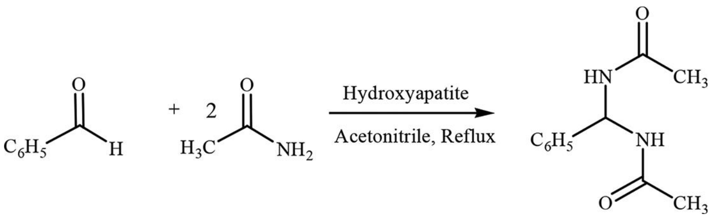
Table 3. Hydroxyapatite catalyzed synthesis of various substitutes bisamides.[a]



Entry	R	R′	Yield (%)	Product	MP (°C) Found	MP (°C) Report (lit)
1	C_6H_5–	CH_3–	95	3a	239–240	239–240[30]
2	C_6H_5–	C_6H_5–	92	3b	243–245	241–243[35]
3	o-OHC_6H_5–	CH_3–	88	3c	225–228	226–228[35]
4	o-OHC_6H_5–	C_6H_5–	90	3d	188–190	191–193[35]
5	$C_6H_5CH{=}CH$–	CH_3–	87	3e	195–197	196–198[35]
6	$C_6H_5CH{=}CH$–	C_6H_5–	91	3f	244–246	246–248[35]
7	p-$NO_2C_6H_5$–	CH_3–	95	3g	271–273	270–272[35]
8	p-$NO_2C_6H_5$–	C_6H_5–	94	3h	265–267	265–267[30]
9	p-BrC_6H_5–	CH_3–	93	3i	244–246	246–248[35]
10	p-BrC_6H_5–	C_6H_5–	94	3j	160–162	162–164[30]
11	p-ClC_6H_5–	CH_3–	92	3k	260–262	258–260[35]
12	p-ClC_6H_5–	C_6H_5–	90	3l	243–245	241–243[35]
13	p-$OCH_3C_6H_5$–	CH_3–	90	3m	222–224	221–222[27]
14	m-$NO_2C_6H_5$–	C_6H_5–	91	3n	228–230	230–232[27]
15	p-$CH_3C_6H_5$–	CH_3–	88	3o	225–226	224–226[27]
16	o-$OCH_3C_6H_5$–	CH_3–	89	3p	226–228	225–228[27]

[a] Reaction conditions: Aldehyde (1 mmol), amide (2 mmol), acetonitirile (2 mL), time (3 h), hydroxyapatite catalyst (50 mg), refluxed conditions.
[b] Isolated yields.

Table 4. Reusablity of hydroxyapatite in the synthesis of *N*,*N*-alkylidene bisamides.[a]



Reuse	1st	2nd	3rd
Yield(%)[b]	95	94%	90

[a]Reaction conditions: Benzaldehyde (1 mmol), acetamide (2 mmol) acetonitrile (2 mL) refluxed for 3 h.
[b]Isolated yield.

Table 5. Comparison with reported catalytic systems for synthesis of bisamides.

Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)	Reusability of catalysts
1	*p*-TSA[27]	100	1	87–99	–
2	Boric acid[28]	Reflux (Toluene solvent)	20–72	32–85	–
3	Phosphotungstic acid[29]	Reflux (Toluene solvent)	20–72	65–94	–
4	SiO_2-PPA[30]	100	1–3	66–83	–
5	Our system[a]	80	3	88–95	3

[a]Reaction conditions. Aldehyde (1 mmol), amide (2 mmol) acetonitrile (3 mL) refluxed for 3 h.

(Table 3, entries 3 and 4). The substrate of *p*-bromobenzaldehyde proceeds smoothly to give the corresponding bisamides in 91% yield (Table 3, entries 9 and 10).

One of the main advantages of heterogeneous catalyst is the recovery and reuse of the catalyst after the reaction. In this connection the reusability of hydroxyapatite for the synthesis of symmetrical bisamides is investigated under same reaction condition. After completion of reaction, catalyst is recovered by simple filtration, washed, dried and reused for next cycle. Even after the third recycle, it exhibits good catalytic activity with 90% yield as shown in Table 4.

The present catalytic system is compared with other reported works based on the reaction conditions used, activity and efficiency for the synthesis of symmetrical bisamide is given in Table 5. The results indicate our catalytic system (entry 5) exhibits better catalytic performance compared to conventional catalysts such as same reaction conditions (entries 2 and 3), higher temperature (entries 1–4), lower yield (entries 2–4) and poor reusability (entries 1–4).

Conclusion

In the present study we describe a practical and inexpensive method for the preparation of symmetrical bisamides through a condensation reaction between aldehydes and amides. Hydroxyapatite has been successfully used as effective catalyst for the synthesis of symmetrical *N*,*N*′-alkylidene bisamides for the first time. This procedure has advantages in competition with the previously reported methods, in terms of yield, green catalyst, mild reaction condition, simple procedure, lack of toxicity, and low cost. The salient feature of this heterogeneous method offers several advantages such as atom efficiently, greener, atom economically, reusability ecofriendly, protocols as the reactions requires neither high temperature nor harsh acids or bases and produces high yields. It suitability with consist of activity for least three cycles is also established, indicating hydroxyapatite is a green catalyst and has potential values for industrial application

Experimental

Preparation of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$

The synthesis of hydroxyapatite (HAp) in powder state is performed by coprecipitation method. 250 ml solution containing 7.93 g of diammonium hydrogen phosphate, maintained at a pH greater than 12, by addition of ammonium hydroxide (60–70) ml, are dropped under constant stirring into 150 ml of a solution containing 23.6 g of calcium nitrate [$Ca(NO_3)_2 4H_2O$]. The suspension is refluxed for 4 h. The hydroxyapatite crystallites are filtered, washed with DDW, dried over night at 80°C and calcined in air at 900 °C for 30 min prior to use. Synthesized hydroxyapatite catalysts are characterized by FT-IR and SEM (see the Supporting Information).

Typical procedure for hydroxyapatite catalyzed synthesis of bisamides

Aldehyde (1 mmol) and amide (2 mmol) are successively added to hydroxyapatite catalyst (50 mg) in 2 mL of acetonitrile solvent then mixture is refluxed for 2–3 h, after completion of the reaction, the mixture is extracted with polar solvent. After removing the catalyst by simple filtration, followed by solvent evaporation the resulting crude product is obtained and purified by column chromatography (silica gel). The purified products are confirmed by their ^{1}H-NMR as well as by melting point data which are all found to be comparable with the reported ones. Full experimental details and ^{1}H NMR, ^{13}C NMR for all compounds can be found in the Supplementary Content section which can be accessed through the articles web page.

Acknowledgements

The authors gratefully acknowledge the financial support from Management of Saiva Bhanu Kshatriya College, Aruppukottai, Tamil Nadu.

References

[1] Santoro, S.; Kozhushkov, S. I.; Ackermann, L.; Vaccaro, L. *Green Chem.* **2016**, 18, 3471.
[2] Schlogl, R. *Angew. Chem.* **2015**, 54, 3465.
[3] Anastas, P. T.; Williamson, T. C. *Oxford University Press, Oxford, Green Chemistry: Frontiers in Chemical Synthesis and Processes (Eds.)*, 2008.
[4] Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, 35, 686.
[5] Sheldon, R.; Arends, I.; Hanefeld, U. *Green Chemistry and Solid Catalysis (Eds.)*, Wiley-VCH: Weinheim, Germany, 2009.
[6] Munnik, P.; de Jongh, P. E.; de Jong, K. P. *Chem. Rev.* **2015**, 115, 6687.
[7] Zhou, C. H. *Appl. Clay. Sci.* **2011**, 53, 85.
[8] Wei, G.; Ma, P. X. *Biomaterials* **2004**, 25, 47, 49.
[9] Cawthray, J. F.; Creagh, A. L.; Haynes, C. A.; Orvig, C. *Inorg. Chem.* **2015**, 54, 1440.
[10] Palmer, L.; Newcom, C.; Kaltz, S.; Spoerke, E.; Stupp, S. *Chem. Rev.* **2008**, 108, 4754.
[11] Li, L.; Pan, H.; Tao, J.; Xu, X.; Mao, C.; Gu, X. *J. Mat. Chem.* **2008**, 18, 4079.
[12] Aoki, H. *Science and Medical Applications of Hydroxyapatite*, JAAS: Tokyo. 1991.
[13] Masuyama, Y.; Sugiokaa, Y.; Chonana, S.; Suzukia, N.; Fujita, M.; Harac, K.; Fukuokac, A. *J. Mol. Catal. A: Chem.* **2012**, 352, 81.

[14] Mori, K.; Yamaguchi, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2001**, 461.

[15] Solhya, A.; Tahir, R.; Sebti, S.; Skouta, R.; Bousmina, M.; Zahouily M.; Larzek, M. *Appl. Catal. A: Gen.* **2010**, 374, 189.

[16] Subramanian, M.; Vanangamudi, G.; Thirunarayanan, G. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* **2013**, 116.

[17] Kantam, M. L.; Balasubrahmanyam, V.; Shiva Kumar, K. B. *Synth. Commun.* **2006**, 36, 1809.

[18] Saha, D.; Chatterjee, T.; Mukherjee, M.; Ranu, B. C. *J. Org. Chem.* **2012**, 77, 9379.

[19] Liu, Y.; Tsunoyama, H.; Akitabc, T.; Tsukuda, T. *Chem. Commun.* **2010**, 46, 550.

[20] Ranu, B. C.; Adak, L.; Chattopadhyay, K. *J. Org. Chem.* **2008**, 73, 5609.

[21] Huang, L.; Luo, P.; Pei, W.; Liu, X.; Wang, Y.; Wang, J.; Xing, W.; Huanga, J. *Adv. Synth. Catal.* **2012**, 354, 2689.

[22] Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, 40, 3405.

[23] Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, 38, 606.

[24] Yamazaki, T.; Nunami, K. I.; Goodman, M. *Biopolymers* **1991**, *3*, 1513.

[25] Yoon, G.; Kang, B. Y.; Cheon, S. H. *Arch. Pharm. Res.* **2007**, 30, 313.

[26] Abbasinejad, M. A.; Mosslemin M. H.; Hassanabadi, A.; Safa, S. T. *Synth. Commun.* **2010**, 1, 2209.

[27] Harichandran, G.; David Amalraja, S.; Shanmugam, P. *J. Iran. Chem. Soc.* **2011**, 1, 298.

[28] Harichandran, G.; David Amalraja, S.; Shanmugam, P. *Indian J. Chem.* **2011**, 50B, 77.

[29] Fernandez, A. H.; Alvarez, R. M.; Abajo, T. M. *Synthesis* **1996**, 1299.

[30] Reza, M.; Shafiee, M. *Journal of Saudi Chemical Society* **2014**, 18, 115.

[31] Subramanian, T.; Pitchumani, K. *Chem Cat Chem* **2012**, 4, 1917.

[32] Subramanian T.; Pitchumani, K. *Catal. Sci, Tech.* **2012**, 2, 296.

[33] Subramanian, T.; Kumar Raja, M.; Pitchumani, K. *J. Mol. Cat. A: Chem.* **2012**, 363–364, 115.

[34] Subramanian, T.; Pitchumani, K. *Catal. Commun.* **2012**, 26, 39–43.

[35] Abbasinejad, M. A.; Mosslemin, M. H.; Hassanabadi, A. *J. Chem. Res.* **2009**, 218.