Tetrahedron Letters 50 (2009) 7220–7222

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Atom-efficient and environment-friendly multicomponent synthesis of amidoalkyl naphthols catalyzed by P_2O_5

Ganesh Chandra Nandi, Subhasis Samai, Ram Kumar, M. S. Singh *

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221 005, India

ARTICLE INFO

Article history:
Received 17 September 2009
Revised 8 October 2009
Accepted 12 October 2009
Available online 29 October 2009

Keywords:
Multicomponent reaction
Amidoalkyl naphthols
P_2O_5
Solvent free one-pot synthesis
Moderate temperature

ABSTRACT

An atom-efficient and environment-friendly approach for the synthesis of amidoalkyl naphthols (**4a–x**) via multicomponent one-pot reaction of 2-naphthol (**1**), aromatic aldehyde (**2**) and amide (**3**) catalyzed by P_2O_5 has been developed. The present approach offers several advantages such as reduced reaction times, moderate temperature, higher yields, eco-friendly reaction condition, easy purification and economic availability of the catalyst.

Multicomponent reactions (MCRs) have been proven to be a very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks, and show high atom-economy, high selectivity and procedural simplicity due to the formation of carbon–carbon and carbon–heteroatom bonds in one-pot.[1] As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from the two-component reactions in several aspects[2] and permitted rapid access to combinatorial libraries of organic molecules for an efficient lead structure identification and optimization in drug discovery.[3] In addition, the implementation of several transformations in a single manipulation is highly compatible with the goals of sustainable and green chemistry.[4]

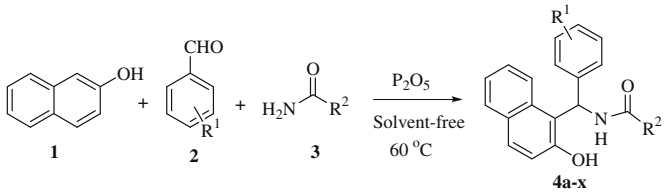
Compounds having 1,3-amino-oxygenated functional groups are present in variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.[5] Moreover, 1-amidoalkyl naphthol can be easily hydrolyzed to 1-aminoalkyl naphthol, which shows biological activities like hypotensive and bradycardiac effect.[6] This 1-aminoalkyl alcohol-type ligand has been used for asymmetric synthesis and also as a catalyst.[7] Several alternative and efficient methods have been developed for the synthesis of amidoalkyl naphthols by multicomponent reaction of 2-naphthol, aldehyde and amide in the presence of different acid catalysts such as montmorillonite K10 clay,[8] $Ce(SO_4)_2$,[9] iodine,[10] $K_5CoW_{12}O_{40}{\cdot}3H_2O$,[11] *p*-TSA,[12] sulfamic acid,[13] $HClO_4$–SiO_2,[14] molten tetraethylammonium chloride,[15] silica sulfuric acid,[16] cation-exchanged resins,[17] $Al(H_2PO_4)_3$,[18a] $Fe(HSO_4)_3$,[18b] $Yb(OTf)_3$,[18c] wet cyanuric chloride,[18d,e] polymer-supported sulfonic acid[18f] and $FeCl_3$–SiO_2.[18g] Hajipour et al.[19] have reported the synthesis of amidoalkyl naphthol in ionic liquid at higher temperature (120 °C). However, some of these protocols suffer from certain drawbacks such as prolonged reaction time, use of dichloromethane like carcinogenic solvent, unsatisfactory yield, high temperature (120–125 °C) and use of toxic, highly acidic and expensive catalysts. Therefore, introducing a clean procedure by the use of green and more eco-friendly catalyst (P_2O_5) with high catalytic activity, moderate temperature and short reaction time accompanied with excellent yield for the production of 1-amidoalkyl-2-naphthols is needed. Phosphorous pentoxide has earlier been widely used for various organic transformations such as Beckmann rearrangement,[20] olefin dimerization,[21] tetrahydropyranylation of alcohols[22] and formation of 1,1-diacetate.[23]

Recently we have reported the reaction of 2-naphthol, aldehyde and active methylene compound such as dimedone or 1,3-dimethylbarbituric acid in the presence of catalyst P_2O_5 or Indium chloride for the formation of benzoxanthene-11-one or benzoanthracene-9,11-dione under solvent-free condition.[24] The reaction proceeds through the in situ formation of *ortho*-quinone methide intermediate,[25] a highly reactive and ephemeral intermediate that has been extensively harnessed by nature. We have now extended our work with the *ortho*-quinone methide intermediate (*o*-QM) using amide as nucleophile for the synthesis of amidoalkyl naphthols.

Herein, we are reporting the multicomponent reaction of 2-naphthol, aldehyde and amide using P_2O_5 as catalyst at 60 °C for the preparation of amidoalkyl naphthols in excellent yield

* Corresponding author. Tel.: +91 542 6702502; fax: +91 542 2368127/9951.
E-mail address: mssinghbhu@yahoo.co.in (M.S. Singh).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.055



Scheme 1. Synthesis of amidoalkyl naphthols.

Table 1
Comparison of P_2O_5 with other catalysts for the synthesis of *N*- [(2-hydroxynaphthalen-1-yl) (3-nitrophenyl)-methyl]acetamide

Entry	Catalyst	Time	Yield (%)	Temp (°C)	Ref
1	$Fe(HSO_4)_3$	25 min	97	85	18b
2	Montmorillonite K10	30 min	96	125	8
3	$K_5CoW_{12}O_{40}{\cdot}3H_2O$	3 h	78	125	11
4	Iodine	5 h	81	125	10
5	$HClO_4.SiO_2$	30 min	95	125	14
6	$Al(H_2PO_4)_3$	17 min	93	125	18a
7	Cation exchange resin	15 min	92	110	17
8	P_2O_5 (10 mol %)	8 h	63	40	—
9	P_2O_5 (10 mol %)	20 min	76	50	—
10	P_2O_5 (5 mol %)	55 min	55	60	—
11	P_2O_5 (10 mol %)	5 min	97	60	—
12	P_2O_5 (15 mol %)	7 min	92	60	—

(Scheme 1). There are no reports on the use of P_2O_5 as catalyst in the synthesis of 1-amidoalkyl-2-naphthols. It has various advantages due to its low toxicity, low price, ease of handling and experimental simplicity.

A test reaction using 2-naphthol, 3-nitrobenzaldehyde and acetamide at 60 °C without catalyst was performed in order to establish the real effectiveness of the catalyst. It was found that no conversion to product was obtained even after 2.5 h of heating. In order to evaluate the appropriate catalyst loading, a model reaction using 2-naphthol, 3-nitrobenzaldehyde and acetamide was carried out using 5 mol %, 10 mol % and 15 mol % of P_2O_5 at 60 °C without solvent (Table 1, entries 10–12). It was found that 10 mol % of catalyst shows maximum yield in minimum time. Higher percentage of loading of the catalyst (15 mol %) neither increases the yield nor lowers the conversion time. So, 10 mol % of catalyst was found to be the optimal quantity and sufficient to push the reaction forward. To explore the generality of the reaction, we extended our study using P_2O_5 (10 mol %) as catalyst under solvent-free condition at 60 °C with different aromatic aldehydes to prepare a series of amidoalkyl naphthols[26] (**4a**–**x**, Table 2). It was found that the use of 1.2 equiv of amide, instead of 1.0 equiv provides a better yield. Various aromatic aldehydes containing electron-withdrawing and electron-donating substituent at *ortho*, *meta* or *para*-positions show equal ease towards the product formation in high yields. The scope of the reaction was also investigated with aliphatic aldehydes and α,β-unsaturated aldehydes. All our attempts with aliphatic aldehydes such as acetaldehyde, butyraldehyde, isobutyraldehyde and α,β-unsaturated aldehydes such as cinnamaldehyde and crotonaldehyde failed to yield the corresponding amidoalkyl naphthols.

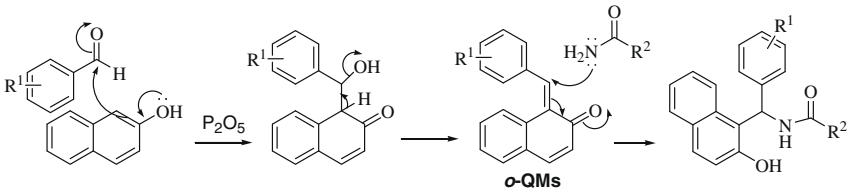
In order to show the accessibility of the present work we have summarized some of the literature results for the preparation of *N*-[(2-hydroxynaphthalen-1-yl)(3-nitro-phenyl)-methyl]acetamide in Table 1, which shows that P_2O_5 is the better catalyst with respect to reaction time and temperature than the reported ones. Encouraged by the successful reaction of aldehydes, 2-naphthol and acetamide under solvent-free condition to give amidoalkyl naphthols (Scheme 1), next we replaced acetamide with benzamide and 2-chloroacetamide where the results were satisfactory. The main advantage of this procedure is the simple work-up, that is, the catalyst and the excess amide were simply washed away with hot water and the residue was crystallized from ethanol to give the pure product.

A mechanistic rationale portraying the probable sequence of events is given in Scheme 2. We supposed that the reaction may proceed via the *ortho*-quinone methides intermediate,[25] which was formed by the nucleophilic addition of 2-naphthol to aldehyde catalyzed by P_2O_5. Subsequent Michael addition of the *o*-QM with the amide afforded the expected amidoalkyl naphthol. The P_2O_5 is supposed to act as water scavenger, which assists the reaction.

In conclusion we have developed an atom-efficient and environment-friendly multicomponent protocol for the synthesis of amidoalkyl naphthols.[26] The remarkable catalytic activity of P_2O_5 is superior to the other reported catalytic methods with respect to shorter reaction times, moderate temperature (60 °C), and the pure products were obtained by simple crystallization from ethanol. The higher yields, mild reaction condition, easy purification

Table 2
P_2O_5-catalyzed synthesis of amidoalkyl naphthols

Entry	R^1	R^2	Product	Time (min)	Yield (%)	Mp (lit. mp)[ref]
1	4-NO_2	$-CH_3$	**4a**	5	96	237–238 (248–250)[14a]
2	3-NO_2	$-CH_3$	**4b**	5	97	256–258 (241–242)[14a]
3	2- NO_2	$-CH_3$	**4c**	7	95	218–219 (180–182)[14a]
4	4-Cl	$-CH_3$	**4d**	5	96	237–238 (230–231)[14b]
5	2-Cl	$-CH_3$	**4e**	6	94	206–207 (213–215)[18b]
6	4-OMe	$-CH_3$	**4f**	5	95	163–164 (183–185)[18b]
7	2-OMe	$-CH_3$	**4g**	7	94	241–242 —
8	4-Me	$-CH_3$	**4h**	5	92	224–225 (222–223)[14a]
9	4-NO_2	$-C_6H_5$	**4i**	10	88	228–229 —
10	3-NO_2	$-C_6H_5$	**4j**	8	89	242–243 (240–242)[18e]
11	2-NO_2	$-C_6H_5$	**4k**	15	85	266–267 —
12	4-Cl	$-C_6H_5$	**4l**	10	90	168–170 (168–170)[14b]
13	2-Cl	$-C_6H_5$	**4m**	15	84	284–285 —
14	4-OMe	$-C_6H_5$	**4n**	10	88	206–208 —
15	2-OMe	$-C_6H_5$	**4o**	15	86	266–267 —
16	H	$-C_6H_5$	**4p**	10	85	238–240 (233–235)[18a]
17	2,4-Cl_2	$-C_6H_5$	**4q**	15	88	262–263 —
18	4-NMe_2	$-C_6H_5$	**4r**	10	85	220–221 —
19	4-Me	$-C_6H_5$	**4s**	10	84	214–215 (215–216)[18e]
20	4-NO_2	$-CH_2Cl$	**4t**	10	85	217–218 —
21	4-Cl	$-CH_2Cl$	**4u**	10	85	198–199 —
22	4-Me	$-CH_2Cl$	**4v**	10	80	174–175 —
23	4-OMe	$-CH_2Cl$	**4w**	10	81	173–174 —
24	H	$-CH_2Cl$	**4x**	10	84	206–207 —



Scheme 2. Tentative mechanism showing the formation of amidoalkyl naphthol.

and economic availability of the catalyst make the eco-friendly procedure an attractive alternative to the existing methods for the synthesis of amidoalkyl naphthols. Further applications of P_2O_5 and *o*-QM intermediate on the extension of this protocol are ongoing in our group.

Acknowledgement

S.S. and G.C.N. are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi for senior research fellowship.

References and notes

1. (a) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187. and references cited therein; (b) Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 8625; (c)For a monograph, see: Zhu, J., Bienayme, H., Eds.Multicomponent Reactions; Wiley-VCH,: Weinheim, Germany, 2005; (d) Domling, A. *Chem. Rev.* **2006**, *106*, 17–89; (e) D'Souza, D. M.; Mueller, T. J. *J. Chem. Soc. Rev.* **2007**, *36*, 3169; (f) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, *73*, 9762; (g) Alizadeh, A.; Mobahedi, F.; Esmaili, A. *Tetrahedron Lett.* **2006**, *47*, 4469; (h) Umkeherer, M.; Kalinski, C.; Kolb, J.; Burdack, C. *Tetrahedron Lett.* **2006**, *47*, 2391; (i) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (j) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (k) Tejedor, D.; Garcia-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484.
2. (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (c) Weber, L.; Illegen, K.; Almstetter, M. *Synlett* **1999**, 366.
3. (a) Weber, L. *Drug Discovery Today* **2002**, *7*, 143; (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51; (c) Tempest, P. A. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 776; (d) Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. *Synlett* **2008**, 4007.
4. For reviews see: (a) Trost, B. M. *Science* **1991**, *254*, 1471; (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.
5. (a) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015; (b) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465; (c) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859; (d) Juaristi, E. In *Enantioselective Synthesis of β-Aminoacids*; John Wiley & Sons: New York, 1997.
6. (a) Dingermann, T.; Steinhilber, D.; Folkers, G. In *Molecular Biology in Medicinal Chemistry*; Wiley-VCH, 2004; (b) Shen, A. Y.; Tsai, C. T.; Chen, C. L. *Eur. J. Med. Chem.* **1999**, *34*, 877; (c) Shen, A. Y.; Chen, C. L.; Lin, C. I. *Chin. J. Physiol.* **1992**, *35*, 45.
7. Hulst, R.; Heres, H.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1373; (b) Li, X.; Yeung, C.-H.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 759.
8. Kantevari, S.; Vuppalapati, S. V. N.; Nagarapu, L. *Catal. Commun.* **2007**, *8*, 1857.
9. Selvam, N. P.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 7481.
10. (a) Das, B.; Laxminarayana, K.; Ravikanth, B.; Rao, B. R. *J. Mol. Catal. A: Chem.* **2007**, *261*, 180; (b) Nagawade, R. R.; Shinde, D. B. *Mendeleev Commun.* **2007**, *17*, 299.
11. Nagarapu, L.; Baseeruddin, M.; Apuri, S.; Kantevari, S. *Catal. Commun.* **2007**, *8*, 1729.
12. Khodaei, M. M.; Khosropour, A. R.; Moghanian, H. *Synlett* **2006**, 916.
13. Patil, S. B.; Singh, P. R.; Surpur, M. P.; Samant, S. D. *Ultrason. Sonochem.* **2007**, *14*, 515.
14. (a) Shaterion, H. R.; Yarahmadi, H.; Ghashang, M. *Tetrahedron* **2008**, *64*, 1263; (b) Mahdavinia, G. H.; Bigdeli, M. A.; Heravi, M. M. *Chin. Chem. Lett.* **2008**, *19*, 1171.
15. Dorehgiraee, A.; Khabazzadeh, H.; Saidi, K. *Arkivoc* **2009**, 303.
16. Srihari, G.; Nagaraju, M.; Murthy, M. M. *Helv. Chim. Acta* **2007**, *90*, 1497.
17. Patil, S. B.; Singh, P. R.; Surpur, M. P.; Samant, S. D. *Synth. Commun.* **2007**, *37*, 1659.
18. (a) Shaterian, H. R.; Amirzadeh, A.; Khorami, F.; Ghashang, M. *Synth. Commun.* **2008**, *38*, 2983; (b) Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 788; (c) Kumar, A.; Rao, M. S.; Ahmad, I.; Khungar, B. *Can. J. Chem.* **2009**, *87*, 714; (d) Mahdavinia, G. H.; Bigdeli, M. A. *Chin. Chem. Lett.* **2009**, *20*, 383; (e) Zhang, P.; Zhan-Hui Zhang, Z.-H. *Monatsh. Chem.* **2009**, *140*, 199; (f) An, L.-T.; Lu, X.-H.; Ding, X.-Q.; Jiang, W.-Q.; Zou, J.-P. *Chin. J. Chem.* **2008**, *26*, 2117; (g) Shaterian, H. R.; Yarahmadi, H. *Tetrahedron Lett.* **2008**, *49*, 1297.
19. Hajipour, A. R.; Ghayeb, Y.; Sheikhan, N.; Ruoho, A. E. *Tetrahedron Lett.* **2009**, *50*, 5649.
20. Ren, R. X.; Zueva, L. D.; Ou, W. *Tetrahedron Lett.* **2001**, *42*, 8441.
21. Hamamatsu, T.; Kimura, N.; Takashima, T.; Morikita, T. Patent USPTO Appln. No. 20090099400—Class: 585529.
22. Eshghi, H.; Shafieyoon, P. *Phosphorous, Sulfur Silicon Relat. Elem.* **2004**, *179*, 2149.
23. Eshghi, H.; Gordi, Z. *Phosphorous, Sulfur Silicon Relat. Elem.* **2004**, *179*, 1341.
24. Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron* **2009**, *34*, 7129.
25. Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.
26. *General procedure for the synthesis of amidoalkylnaphthol*: To a nicely ground mixture of 2-naphthol (1.0 mmol), aldehyde (1.0 mmol) and amide (1.2 mmol), the catalyst P_2O_5 (10 mol %) was added and the reaction mixture was heated at 60 °C for the stipulated period of time. Completion of the reaction was checked by TLC. Hot water was added to the reaction mixture to remove the unreacted amide and catalyst. The crude product obtained was crystallized from ethanol to give the pure compound.