Tetrahedron Letters 51 (2010) 2629–2632

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of triazolo indazolones using 3D mesoporous aluminosilicate catalyst with nanocage structure

M. Adharvana Chari [a], G. Karthikeyan [a,b,d], A. Pandurangan [d], T. Siddulu Naidu [a], B. Sathyaseelan [a,b], S. M. Javaid Zaidi [c], A. Vinu [a,*]

[a] International Center for Materials Nanoarchitectonics, WPI Research Center, National Institute for Materials Science, 1-1 Namiki, Tsukuba 305-0044, Japan
[b] Department of Chemistry, Anna University, Chennai 600 025, India
[c] The Center of Research Excellence in Renewable Energy (CoRERE), Chemical Engineering Department, King Fahd University of Petroleum & Minerals, Dhahran 31261, Saudi Arabia
[d] Institute of Catalysis & Petroleum Technology, A.C. College of Technology, Anna University, Chennai 600025, India

ARTICLE INFO

Article history:
Received 13 January 2010
Revised 3 March 2010
Accepted 8 March 2010
Available online 11 March 2010

Keywords:
Dimedone
Urazole
Aromatic aldehyde
One-pot condensation
AlKIT-5
Indazole-1,3,8-trione derivatives

ABSTRACT

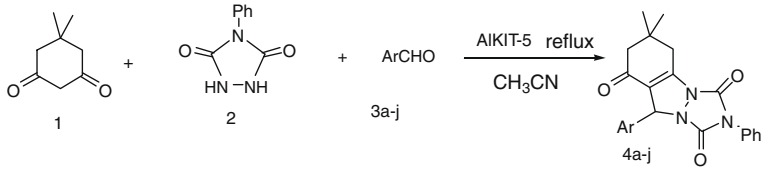
Mesoporous Aluminosilicate (AlKIT-5) has been found to be an efficient catalyst for one-pot synthesis of triazolo[1,2-a]indazole-1,3,8-trione derivatives from dimedone, urazole, and aromatic aldehydes using acetonitrile as a solvent. This new method is simple, effective, ecofriendly, and consistently has the advantage of excellent yields (80–96%) and short reaction time (30–60 min). The effect of the catalyst weight, aluminum content in the catalyst, and the solvents on the synthesis of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives has been investigated. It has been found that the catalyst can be recycled for several times without much affecting its activity for a variety of organic transformations.

Multicomponent reactions (MCRs)[1–3] offer significant benefits such as saving energy, time, money, and raw materials over conventional linear-step syntheses. MCRs are economically and environmentally very advantageous and help to avoid the usage of expensive, toxic, and hazardous solvents as the multi-step synthesis involves various steps which produce considerable amount of wastes due to isolation and separation of the products after each step. Among the various MCR products, triazolo[1,2-*a*]indazole-1,3,8-triones[4,5] are very important class of nitrogen-containing heterocyclic compounds which exhibit high biological activity and are critical for enhancing the quality of life.[6–10] Heterocycles containing a urazole (1,2,4-triazolidine-3,5-diones) and its derivatives also exhibit anticonvulsant and fungicidal activities.[11–17] As these molecules posses excellent biological activities, much attention has been given to the synthesis of urazole and its derivatives in the recent years.[18–22] Several reports have been published on the synthesis of heterocycles containing an urazole moiety.[18–22] Triazolo[1,2-*a*]indazole-1,3,8-trione derivatives are generally synthesized by the condensation of dimedone, urazole, and aromatic aldehydes under acetonitrile using homogeneous catalysts such as *p*-toluene sulfonic acid. Although the homogenous catalysts work better in the above process, they suffer from one or more disadvantages such as high cost, the requirement of huge amount of catalyst, regeneration of the catalyst, and the separation of the product from the reaction mixtures. Therefore, the search continues for a better catalyst for the synthesis of indazole-1,3,8-trione derivatives.

In organic synthesis, the use of heterogeneous catalysts, especially mesoporous materials,[23,24] has received considerable importance in recent years. Among the various heterogeneous mesoporous silica catalysts, mesoporous catalysts with 3D structures are more advantageous for the synthesis of organic molecules than the catalysts with 1D mesoporous structure because the former provide more adsorption sites and resistant to pore blocking and allow easy diffusion of the reactant molecules. Very recently, we have reported the synthesis of 3D aluminum-supported mesoporous KIT-5 material (AlKIT-5) which is highly acidic and possesses 3D mesostructure with *Fm*3*m* symmetry and large cage-type pores.[25] AlKIT-5 was applied to various acid-catalyzed reactions. It was found that the catalytic activity of AlKIT-5 is much superior to the other mesoporous and microporous catalysts.[25–31] Although these materials possess interesting textural and catalytic properties, unfortunately, with the best of our knowledge, there has been no report available on the synthesis of indazole-1,3,8-triones using such materials as catalysts till now. Here we report an efficient, simple one-pot, and three-component method for the preparation of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives by condensation of 5,5-dimethylcyclohexane-1,3-dione (dimedone,

* Corresponding author. Tel.: +81 298604563; fax: +81 298604706.
E-mail address: vinu.ajayan@nims.go.jp (A. Vinu).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.03.021



Scheme 1. Synthesis of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives using AlKIT-5 as catalyst.

Table 1
Effect of the weight and catalytic activity of the AlKIT-5 catalysts on the synthesis of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives

S.No	Catalyst	Wt of the catalyst (mg)	Dp_{ads}, BJH (nm)	Acidity (mmol/g)	Yield (%)
1	AlKIT-5(10)	50	6.0	0.50	34
2	AlKIT-5(10)	100	6.0	0.50	72
3	AlKIT-5(10)	150	6.0	0.50	96
4	AlKIT-5(10)	200	6.0	0.50	96
5	AlKIT-5(28)	150	5.6	0.32	89
6	AlKIT-5(44)	150	5.2	0.14	78
7	Montimorillonite K-10	150	—	—	80
8	Nafian	150	—	—	84
9	Amberlyst-15	150	—	—	90

Reaction conditions: substrate: dimedone, urazole, and aromatic aldehyde, reaction time: 30 min, reaction temperature: reflux, solvent: acetonitrile, Dp: pore diameter. AlKIT-5(10): the number in the parentheses denotes the n_{Si}/n_{Al} ratio of the final product.

1) urazole (**2**) and aromatic aldehydes (**3**) under acetonitrile reflux conditions using AlKIT-5 as the catalyst.

Initially we studied the catalytic properties of AlKIT-5 using dimedone (**1**), urazole (**2**), and aromatic aldehyde (**3a–j**) (Scheme 1). The effect of the amount of catalyst on the synthesize of the triazolo[1,2-*a*]indazole-1,3,8-trione derivatives was studied and the results are given in Table 1. It was found that the yield of the final products increases with increasing amount of the

Table 2
AlKIT-5-catalyzed synthesis of triazolo[1,2-a]indazole-1,3,8-trione derivatives

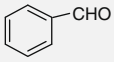
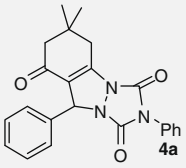
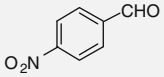
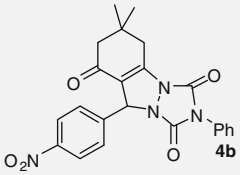
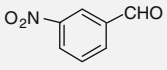
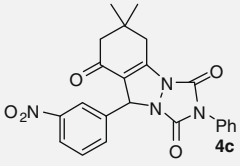
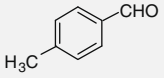
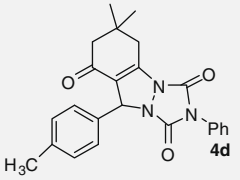
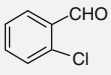
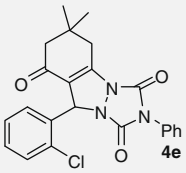
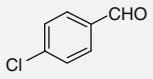
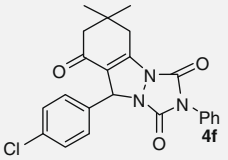
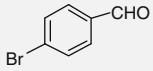
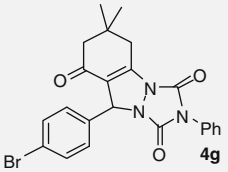
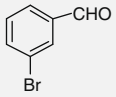
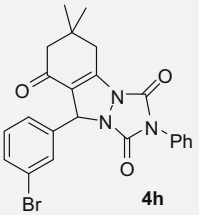
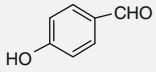
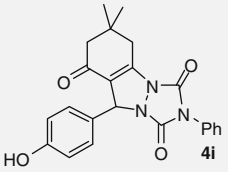
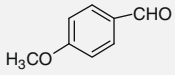
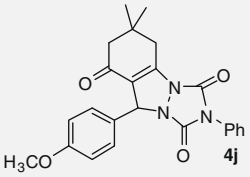
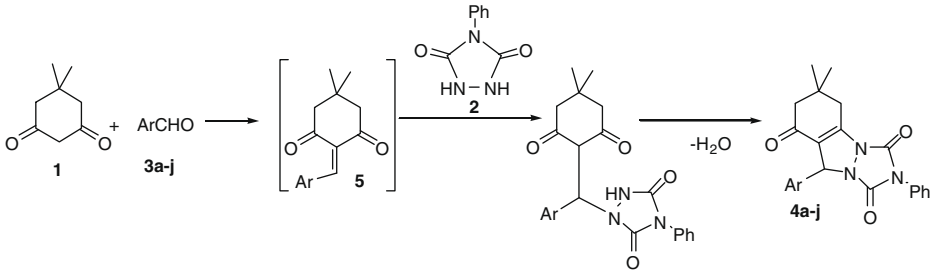
S.No	Aldehyde	Product	Time (min)	Yield(%)
1		 **4a**	30	96
2		 **4b**	30	96
3		 **4c**	60	88
4		 **4d**	60	90
5		 **4e**	60	85

Table 2 (*continued*)

S.No	Aldehyde	Product	Time (min)	Yield(%)
6		 **4f**	60	84
7		 **4g**	60	83
8		 **4h**	60	80
9		 **4i**	60	82
10		 **4j**	60	82



Scheme 2. Mechanism for the formation of triazolo, indazole-triones.

catalyst in the reaction mixture. The yield of the final product increases from 34% to 96% with increasing catalyst weight from 50 to 200 mg. To optimize the synthetic conditions of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives, we have chosen the entry **1** given in Table 2, and used AlKIT-5 catalyst with different n_{Si}/n_{Al} ratios. It was found that the amount of Al in the framework significantly alters the yield of the final product. Among the AlKIT-5 catalyst with different n_{Si}/n_{Al} ratios, AlKIT-5 with a n_{Si}/n_{Al} ratio of 10 was found to be highly active mainly due to its high acidity and large surface area. It should be mentioned that AlKIT-5 with a n_{Si}/n_{Al} ratio of 10 gave the yield of the product **4a** almost 96% in 30 min time. The activity of the standard catalysts such as Nafian, Amberlyst, and Monmorillonite K-10 has been tested and the results have been compared with that of the AlKIT-5(10). It has been found that the activity of the AlKIT-5(10) is better as compared to that of those commercially available catalysts.

We have also carried out the synthesis[32] of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives using various aromatic aldehydes with dimedone and urazole in the presence of 150 mg of AlKIT-5 at reflux temperature for 30–60 min under acetonitrile solvent. Most of the cases, ca. 80–96% yield of the final products was obtained using the AlKIT-5 catalyst under acetonitrile conditions (Table 2). The products **4a-j** formed by initial formation of heterodiene **5** by standard Knoevenagel condensation of dimedone **1** and aldehyde **3a**–**j**. Subsequent Michael-type addition of urazole **2** to heterodiene **5** followed by cyclization afforded the corresponding product **4a–j** and water (Scheme 2). The results were good in terms of yields and product purity in the presence of AlKIT-5 whereas only less than 25% yield of the final product was obtained when the reactions were carried out without any catalyst over a long period of time (5–6 h). All synthesized products (**4a–j**) were stable and characterized by using IR, ^{1}H NMR, and mass spectral analysis and

also by comparison with authentic samples. Aliphatic aldehydes were also utilized for the synthesis of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives. Unfortunately, the catalyst was almost inactive under the same reaction conditions for the aliphatic aldehydes.

We also investigated the role of solvents on the synthesis of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives using AlKIT-5 catalysts. Among the various solvents such as methylene chloride, THF, acetonitrile, and methanol used for this transformation, acetonitrile and methanol were found to be the best solvents. Recycling experiments were conducted to find out the stability of the catalyst after the reaction. The catalyst was easily separated by centrifugation and reused after activation at 500 °C for 3–4 h in air. The efficiency of the recovered catalyst was verified with the entry **1** given in Table 2. Using the fresh catalyst, the yield of product (**4a**) was 96%, while the recovered catalyst in the three subsequent recyclization gave the yields of 94%, 92%, and 91%, respectively. These results reveal that the catalyst can be recycled several times without losing much activity. In addition, we have carried out scale-up experiments with 1 gm of benzaldehyde, (Table 2, entry a) using AlKIT-5 catalyst and we achieved 95% of the yield which is almost nearer to the reported yield given in Table 2 (entry a), revealing that the process can easily be commercialized with our catalyst.

In summary, we have developed a new methodology for the one-pot, three-component synthesis of triazolo, indazole-trione derivatives by cyclocondensation reaction of dimedone, urazole, and aromatic aldehydes in the presence of AlKIT-5 catalyst under acetonitrile solvent conditions at reflux temperature. The catalyst was found to be highly active for the synthesis of triazolo[1,2-*a*]indazole-1,3,8-trione derivatives which can be prepared from available inexpensive reagents and can be easily recycled. This method is quite simple, high yielding, time saving, and ecofriendly process.

Acknowledgments

This work was financially supported by the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) under the Strategic Program for Building an Asian Science and Technology Community Scheme and World Premier International Research Center (WPI) Initiative on Materials Nanoarchitectonics, MEXT, Japan. One of the Authors thank Mr. Bello for the technical assistance.

References and notes

1. *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; p 95.
2. Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
3. Domling, A. *Chem. Rev.* **2006**, *106*, 17.
4. Menard, C.; Doris, E.; Mioskowski, C. *Tetrahedron Lett.* **2003**, *44*, 6591.
5. Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 8790.
6. Noga, E. J.; Barthalmus, G. T.; Mitchell, M. K. *Cell Biol. Int. Rep.* **1986**, *10*, 239.
7. Craig In, P. N.; Drayton, C. J.. In *Comprehensive Medicinal Chemistry*; Pergamon Press: New York, 1991; Vol. 8.
8. Awadallah, F. M.; Müller, F.; Lehmann, A. H.; Abadi, A. H. *Bioorg. Med. Chem.* **2007**, *15*, 5811.
9. Bagley, M. C.; Davis, T.; Dix, M. C.; Rokicki, M. J.; Kipling, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5107.
10. Conchon, E.; Anizon, F.; Aboab, B.; Prudhomme, M. *J. Med. Chem.* **2007**, *50*, 4669.
11. Izydore, R. A.; Bernal-Ramirez, J. A.; Singh, P. *J. Org. Chem.* **1990**, *55*, 3761.
12. Kiriazis, A.; Ruffer, T.; Jantti, S.; Lang, H.; Yli-Kauhaluama, J. *J. Comb. Chem.* **2007**, *9*, 263.
13. Kolb, V. M.; Dworkin, J. P.; Miller, S. L. *J. Mol. Evol.* **1994**, *38*, 549.
14. Lei, X.; Zaarur, N.; Sherman, M. Y.; Porco, J. A., Jr. *J. Org. Chem.* **2005**, *70*, 6474.
15. Boatman, P. D.; Urban, J.; Nguyen, M.; Qabar, M.; Kahn, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1445.
16. Jacobson, C. R.; D'Adamo, A.; Cosgrove, C. E. U.S. Patent 3,663,564, 1972.
17. Shgematsu, T.; Tomita, M.; Shibahara, T.; Nakazawa, M.; Munakata, S. JP. Patent 52,083,562, 1977.
18. Tanaka, S.; Seguchi, K.; Itoh, K.; Sera, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2335.
19. Meehan, S.; Little, R. D. *J. Org. Chem.* **1997**, *62*, 3779.
20. Deghati, P. Y. F.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron Lett.* **1998**, *39*, 4561.
21. Boldi, A. M.; Johnson, C. R.; Eissa, H. O. *Tetrahedron Lett.* **1999**, *40*, 619.
22. Arroya, Y.; Rodriguez, J. F.; Santos, M.; Sanz Tejedor, M. A.; Vaco, I.; Garcia, R. J. L. *Tetrahedron: Asymmetry* **2004**, *15*, 1059.
23. Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952.
24. Chari, M. A.; Syamasundar, K. *Catal. Commun.* **2005**, *6*, 67.
25. Srinivasu, P.; Alam, S.; Balasubramanian, V. V.; Velmathi, S.; Sawant, D. P.; Bohlmann, W.; Mirajkar, S. P.; Ariga, K.; Halligudi, S. B.; Vinu, A. *Adv. Funct. Mater.* **2008**, *18*, 640.
26. Chakravarti, R.; Kalita, P.; Tamil Selvan, S.; Oveisi, H.; Balasubramanian, V. V.; Lakshmi Kantam, M.; Vinu, V. *Green Chem.* **2010**, *12*, 49.
27. Shobha, D.; Chari, M. A.; Mano, A.; Selvan, S. T.; Mukkanti, K.; Vinu, A. *Tetrahedron* **2009**, *65*, 10608.
28. Vinu, A.; Kalita, P.; Balasubramanian, V. V.; Oveisi, H.; Tamil Selvan, T.; Mano, A.; Chari, M. A.; Subba Reddy, B. V. *Tetrahedron Lett.* **2009**, *50*, 7132.
29. Chakravarti, R.; Kalita, P.; Pal, R. R.; Halligudi, S. B.; Lakshmi Kantam, M.; Vinu, A. *Micropor. Mesopor. Mater.* **2009**, *123*, 338.
30. Balasubramanian, V. V.; Srinivasu, P.; Anand, C.; Pal, R. R.; Ariga, K.; Velmathi, S.; Alam, S.; Vinu, A. *Micropor. Mesopor. Mater.* **2008**, *114*, 303.
31. Shobha, D.; Chari, M. A.; Tamil Selvan, S.; Oveisi, H.; Mano, A.; Mukkanti, K.; Vinu, A. *Micropor. Mesopor. Mater.* **2010**, *129*, 112.
32. *General procedure for the synthesis of triazoloindazole-triones* (**4a–j**): A mixture of dimedone (**1**) (1 mmol), urazole (**2**) (1 mmol), aromatic aldehyde (**3**) (1.2 mmol), and AlKIT-5 (150 mg) was stirred in acetonitrile at reflux temperature until thin layer chromatography indicated the completion of the reaction. After the completion of the reaction, 20 ml of ethyl acetate was added to the reaction mixture and the catalyst was recovered by filtration. The organic layer was concentrated and the crude product was purified by silica gel column chromatography using ethyl acetate–*n*-hexane (1:3) as eluent to afford the desired product (**4**). Spectral data are in full agreement with the data reported in the literature [5] and the spectral data of some compounds are given below. Entry 1 (**4a**): White solid (96%), mp 187–189 °C. IR (KBr) (ν_{max}/cm^{-1}): 2955, 1779, 1735, 1652.; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.21 (6H, s, $2CH_3$), 2.36 (2H, s, CH_2), 2.94 (2H, AB system, $^2J_{HH}$ = 18.0 Hz, CH_2), 6.24 (1H, s, CH), 7.36–7.48 (10H, m, H-Ar). EIMS: *m*/*z* [M$^+$] = 387. Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.22; H, 5.39; N, 10.93. Entry 10 (**4j**): White solid (82%); mp 165–167 °C. IR (KBr) (ν_{max}/cm^{-1}): 2947, 1782, 1723, 1668. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.21 (6H, s, $2CH_3$), 2.10 (3H, s, CH_3) 2.40 (2H, s, CH_2), 2.92 (2H, s, CH_2), 6.19 (1H, s, CH), 7.20–7.49 (9H, m, H-Ar); EIMS: *m*/*z* [M$^+$] = 417; Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.06; H, 5.51; N, 10.08. Found: C, 69.05; H, 5.50; N, 10.06.