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An Efficient One-pot Synthesis of 2-Amino-5-arylidenethiazol-4-ones Catalyzed by MgO Nanoparticles

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A mild and efficient protocol for the synthesis of 2-amino-5-arylidene-1,3-thiazol-4(5H)-ones is reported by three component reaction of aldehydes, rhodanine and secondary amines in the presence of magnesium oxide nanoparticles as heterogeneous nanocatalyst in good yields and short reaction times.

Keywords: Multicomponent reaction; Rhodanine; MgO nanoparticles; Knoevenagel condensation; 2-Amino-5-arylidene-thiazol-4-one.

INTRODUCTION

4-Thiazolidinones are considered as privileged structures in the medicinal chemistry field.[1-3] Particularly 2-amino-5-arylidene-1,3-thiazol-4(5H)-ones have been widely investigated for a range of pharmacological activities such as antibacterial,[4,5] antiviral,[6] cardiotonic[7,8] and anti-inflammatory activities.[9,10] Numerous synthetic routes[11-21] have been developed in order to obtain this heterocyclic core, but these described routes require additional steps with extended reaction times, high temperatures, and laborious work-up. In recent years, Anderluh et al. reported an acid catalyzed microwave assisted three component synthesis of 2-amino-5-alkylidenethiazol-4-ones,[22] which requires high temperature (~150 °C) microwave heating and double equivalent of aldehydes for good yield. Therefore, this method is no longer a green methodology.

Metal oxide nanoparticles have been found excellent applications as catalysts in the synthesis of organic compounds.[23-25] Their high reactivity is due to their limited size and a high density of corner or edge surface sites.[26,27] Among them, magnesium oxide nanoparticle (MgO-NPs) is most widely used as heterogeneous catalyst and exhibits high activities in numerous base-catalyzed organic reactions.[28-30] In continuation of our previous works for the synthesis of novel biologically interested heterocyclic compounds,[31-33] we report herein a novel, efficient and convenient one-pot synthesis of a variety of 2-amino-5-alkylidene-thiazol-4-ones using MgO-NPs as heterogeneous catalyst (Scheme I).

RESULTS AND DISCUSSION

In order to determine the best reaction conditions, the model reaction of benzaldehyde (1 mmol), rhodanine (1 mmol), and morpholine (1 mmol) was optimized under a variety of conditions and the results are summarized in Table 1. The reaction was first tried under catalyst free conditions and the result indicated that presence of catalyst is necessary for this transformation (Table 1, entry 1). Then, the reaction was examined in the presence of different base catalysts under diffrerent conditions. The optimal result was obtained when 30 mol% of MgO-NPs had been used in aqueous ethanol at 50 °C (Table 1, entry 9). After optimization of the model reaction, a variety of 2-amino-5-arylidenethiazol-4-ones were synthesized with three-component reaction of rhodanine (1 equiv, 1 mmol), secondary amines (1 equiv, 1 mmol), and some benzaldehydes with various functionalities (1 equiv, 1 mmol) in according to Scheme II. The products were obtained in excellent yields with high purity (Table 2). The structures of products were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis, and were found to be identical with the data described in the literature.[19-22] The reaction was also examined in the presence of some aliphatic aldehydes, but the desired products were not obtained.

Scheme I Preparation of 2-amino-5-arylidenethiazol-4-ones

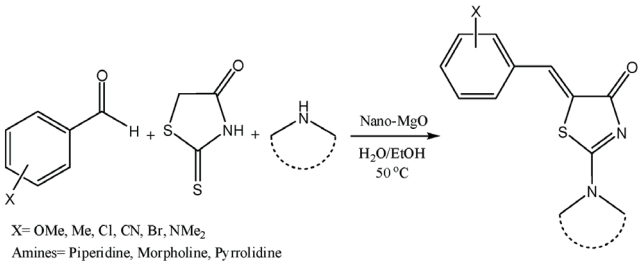

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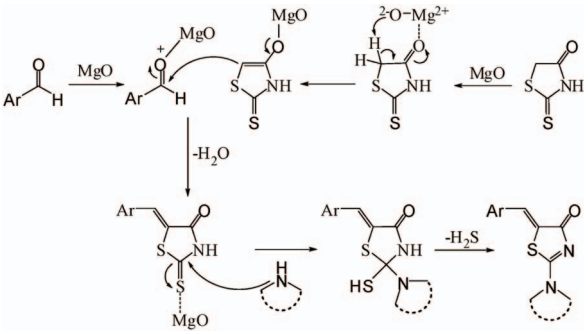
Table 1. Optimization of reaction conditions[a]

Entry	Catalyst (mol%)	Solvent	Time (min)	Yield (%)
1	-	H_2O+EtOH	250	10
2	NaOH (50)	H_2O+EtOH	30	10
3	K_2CO_3 (50)	H_2O+EtOH	25	10
4	DBU (50)	H_2O+EtOH	35	15
5	ZnO-NPs (50)	H_2O+EtOH	150	61
6	TiO_2-NPs (50)	H_2O+EtOH	140	58
7	Bulk MgO (50)	H_2O+EtOH	170	52
8	MgO-NPs (50)	H_2O+EtOH	110	95
9	MgO-NPs (30)	H_2O+EtOH	120	95
10	MgO-NPs (20)	H_2O+EtOH	140	82
11	MgO-NPs (30)	Dry EtOH	210	68
12	MgO-NPs (30)	THF	165	47
13	MgO-NPs (30)	H_2O	110	71
14	MgO-NPs (30)	DCM	120	65

[a] Reaction and conditions: rhodanine (1 equiv, 1 mmol), benzaldehyde (1 equiv, 1 mmol), morpholine (1 equiv, 1 mmol), different catalysts, 50 °C, stirring.

A plausible mechanism for the formation of products is given in Scheme II. During the process, the Knoevenagel condensation between aldehyde and rhodanine should first take place as evidenced by the isolation of an 5-arylidene thiazol-4-one intermediate after the reaction proceeding for a few minutes. The quenching of the reaction could simply be done by removing the catalyst from the reaction mixture through filtration. Since the catalyst is heterogeneous, it remains outside the homogeneous phase, and the starting

Scheme II Proposed mechanism of preparation of 2-amino-5-arylidene-thiazol-4-ones



materials will be in the homogeneous phase of aqueous ethanol. This three-component reaction proceeds *via* dual activation of substrates by MgO-NPs which have a number of anionic oxidic Lewis basic (O^{2-}/O^{-}) and hydroxylic Bronsted basic (OH) sites along with Mg^{2+} as Lewis acid site.[28] The Lewis base moiety of the catalyst activates the methylene group of rhodanine. The carbonyl oxygen of aldehyde coordinates with the Lewis acid moiety increasing the electrophilicity of the carbonyl carbon and thereby making it possible to carry out the reaction in short time.

In conclusion we have developed an efficient protocol for the three-component synthesis of 2-amino-5-arylidenethiazol-4-ones from rhodanine, amines and aldehyde in the presence of MgO-NPs as heterogeneous catalyst. This new method offers several advantages such as excel-

Table 2. Preparation of 2-amino-5-arylidenethiazol-4 ones[a]

Entry	Product	Aldehyde	Amine	Time (min)	Melting point (°C)	Yield (%)[b]
1	4a	PhCHO	piperidine	95	213-215	91
2	4b	PhCHO	pyrrolidine	45	219-220	80
3	4c	PhCHO	morpholine	105	194-196	95
4	4d	4-CN-PhCHO	piperidine	120	192-194	82
5	4e	4-CN-PhCHO	pyrrolidine	100	256-260	78
6	4f	4-CN-PhCHO	morpholine	50	271-273	76
7	4g	4-Cl-PhCHO	morpholine	120	236-238	90
8	4h	4-Cl-PhCHO	piperidine	100	207-209	89
9	4i	2-MeO-PhCHO	piperidine	85	163-165	84
10	4j	4-Me-PhCHO	piperidine	110	152-154	93
11	4k	4-OMe-PhCHO	piperidine	95	197-199	81
12	4l	2-Br-PhCHO	piperidine	100	162-164	89
13	4m	2-Br-PhCHO	morpholine	110	234-236	94
14	4n	2-Br-PhCHO	pyrrolidine	75	210-212	85
15	4o	2-Cl-PhCHO	pyrrolidine	90	236-238	87
16	4p	4-(NMe_2)-PhCHO	pyrrolidine	80	228-230	87

[a] Reaction and conditions: benzaldehyde derivatives (1 equiv, 1 mmol), rhodanine (1 equiv, 1 mmol), amines (1 equiv, 1 mmol), MgO-NPs (0.3 eq, 0.15 mmol), H_2O + EtOH (1:1), 50 °C, stirring.
[b] Isolated yield.

lent yields, short reaction times, mild conditions and easy work-up.

EXPERIMENTAL

General: All chemicals and reagents were purchased from Fluka and Merck and used without further purification. Magnesium Oxide nanoparticles (20 nm diameters, SSA: >60 M^2/g) were obtained from US Research Nanomaterials, Inc. (USA). Melting points were measured on an Electrothermal 9100 apparatus. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for 1H, 100.6 MHz for 13C) with $CDCl_3$ or DMSO-d6 as solvent. IR spectra were recorded on an FT-IR Bruker vector 22 spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried with a Perkin-Elmer 2400II CHNS/O Elemental Analyzer. **General procedure for the synthesis of 2-amino-5- arylidenethiazol-4-ones:** A mixture of rhodanine (1 mmol), amine (1 mmol), aldehyde (1 mmol) and 12 mg (30 mol %) of MgO-NPs in 4 mL aqueous ethanol (50:50) were stirred in 50 °C until the reaction is completed. The completion of the reaction was indicated by the disappearance of the starting material in thin layer chromatography. After completion of the reaction, the crude product was filtered and the residue was taken in DCM and filtered again to separate the product as filtrate from the catalyst. The product was further purified by recrystallization in EtOAc/DCM (equal volume). **Isolation of 5-arylidene thiazol-4-one intermediate:** A mixture of rhodanine (1 mmol), amine (1 mmol), aldehyde (1 mmol) and 12 mg (30 mol %) of MgO-NPs in 4 mL aqueous ethanol (50:50) were stirred in 50 °C. After 5-10 minutes, the reaction mixture was filtered and the residue was taken in DCM and filtered again to separate the product as filtrate from the catalyst. Finally, the solvent was evaporated from the product in a rotary evaporator. Data of selected products are represented below. **5-Benzylidene-2-(piperidin-1-yl)thiazol-4(5H)-one (4a):** Yield 849 mg, 91%; yellow powder; mp 213-215 °C; IR (KBr, cm^{-1}) ν_{max}: 2939, 1700, 1673, 1612, 1560; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69-1.81 (6H, m, $3CH_2$), 3.59 (2H, br s, CH_2), 4.01-4.04 (2H, m, CH_2), 7.36-7.40 (1H, m, CH_{Ar}), 7.43-7.47 (2H, m, CH_{Ar}), 7.54 (d, 2H, $^1J_{HH}$ = 7.2 Hz, CH_{Ar}), 7.81 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 25.5, 26.2, 49.7, 50.3, 128.3, 129.0, 129.6, 129.7, 131.2, 134.4, 174.6, 181.1; MS (ESI): *m/z* 272 ($M^{+\cdot}$); Anal. Calcd for $C_{15}H_{16}N_2OS$ (272.37): C, 66.15; H, 5.92; N, 10.29; S, 11.77. Found: C, 66.46; H, 5.87; N, 10.50; S, 11.82. **5-(4-Chlorobenzylidene)-2-morpholinothiazol-4(5H)-one (4g):** Yield 90%; yellowish white powder; m.p. 236-238 °C; IR (KBr) (ν, cm^{-1}): 3049, 2962, 1683, 1573, 1257; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (t, J = 5.1 Hz, 2H, CH_2), 3.78-3.85 (m, 4H, $2CH_2$), 4.07 (t, J = 4.8 Hz, 2H, CH_2), 7.40-7.47 (m, 4H, $4CH_{arom.}$), 7.72 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.1, 66.3, 66.4, 128.6, 129.1, 130.0, 130.7, 132.6, 135.5, 175.0, 180.5; MS: *m/z* 310 ($M^{+\cdot}$+1), 308 ($M^{+\cdot}$); Anal. Calcd for $C_{14}H_{13}ClN_2O_2S$ (308.78): C, 54.46; H, 4.24; N, 9.07; S, 10.38. Found: C, 54.22; H, 4.29; N, 9.15; S, 10.27.

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REFERENCES

1. Lesyk, R. B.; Zimenkovsky, B. S.; Kaminskyy, D. V.; Kryshchyshyn, A. P.; Ya Havryluk, D.; Atamanyuk, D. V.; Yu, Subtel'na I.; Khyluk, D. V. *Biopolym. Cell.* **2011**, *27*, 107.
2. Lesyk, R. B.; Zimenkovsky, B. S. *Curr. Org. Chem.* **2004**, *8*, 1547.
3. Prabhakar, Y. S.; Solomon, V. R.; Gupta, M. K.; Katti, S. B. *Top. Heterocycl. Chem.* **2006**, *50*, 161.
4. Yanan, H.; Helm, J. S.; Chen, L.; Ginsberg, C.; Gross, B.; Kraybill, B.; Tiyanont, K.; Fang, X.; Wu, T.; Walker, S. *Chem. Biol.* **2004**, *11*, 703.
5. Kocabalkanlia, A.; Ates, Ö.; Ötükb, G. *Arch. Pharm.* **2001**, *334*, 35.
6. Abdel-Ghani, E. J. *Chem. Res. Synop.* **1999**, *3*, 174.
7. Andreani, A.; Rambaldi, M.; Leoni, A.; Locatelli, A.; Bossa, R.; Chiericozzi, M.; Galatulas, I.; Salvatore, G. *Eur. J. Med. Chem.* **1996**, *31*, 383.
8. Andreani, A.; Rambaldi, M.; Locatelli, A.; Leoni, R.; Bossa, M.; Chiericozzi, I.; Galatulas, G.; Salvatore, A. *Eur. J. Med. Chem.* **1993**, *28*, 825.
9. Nasr, M. N. A.; Said, S. A. *Arch. Pharm.* **2003**, *336*, 551.
10. Song, Y.; Connor, D. T.; Doubleday, R.; Sorenson, R.; Sercel; R. J.; Unangs, A. D.; Bruce, P. C.; Roth, D. *J. Med. Chem.* **1999**, *42*, 1151.
11. Khare, R. K.; Srivastava, M. K.; Singh, H. *Indian J. Chem. Sect. B* **1995**, *34*, 828.
12. Hendrickson, J. B.; Rees, R.; Templeton, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 107.
13. Hurst, D. T.; Atcha, S.; Marshall, K. L. *Aust. J. Chem.* **1991**, *44*, 129.
14. Sarodnick, G.; Heydenreich, M.; Linker, T.; Kleinpeter, E. *Tetrahedron* **2003**, *59*, 6311.
15. Seebacher, W.; Belaj, F.; Saf, R.; Brun, R.; Weis, R. *Monatsh. Chem.* **2003**, *134*, 1623.
16. Iwataki, I. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3218.
17. Roessler, A.; Boldt, P. *Synthesis* **1998**, *1998*, 980.
18. Taylor, E. C.; Wolinsky, J.; Lee, H. H. *J. Am. Chem. Soc.* **1954**, *76*, 1870.
19. Pulici, M.; Quartieri, F. *Tetrahedron Lett.* **2005**, *46*, 2387.

20. Mukhopadhyay, C.; Ray, S. *Tetrahedron Lett.* **2011**, *52*, 6431.
21. Bourahla, K.; Derdour, A.; Rahmouni, M. *Tetrahedron Lett.* **2007**, *48*, 5785.
22. Anderluh, M.; Jukič, M.; Petrič, R. *Tetrahedron* **2009**, *65*, 344.
23. Verduraz, F. B.; Fievet, F.; Piquemal, J. Y.; Brayner, R.; El Kabouss, K.; Soumare, Y.; Viau, G.; Shafeev, G. *Braz. J. Phys.* **2009**, *39*, 134.
24. Rahimizadeh, M.; Bakhtiarpoor, Z.; Eshghi, H.; Pordel, M.; Rajabzadeh, G. *Monatsh. Chem.* **2009**, *140*, 1465.
25. Bhattacharyya, P.; Pradhan, K.; Paul, S.; Das, A. R. *Tetrahedron Lett*. **2012**, *53*, 4687.
26. Wagner, G. W.; Bartram, P. W.; Koper, O.; Klabunde, K. J. *J. Phys. Chem. B* **1999**, *103*, 3225.
27. Wagner, G. W.; Procell, L. R.; Connor, R. J.; Munavalli, S.; Carnes, C. L.; Kapoor, P. N.; Klabunde, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 1636.
28. Karmakar, B.; Banerji, J. *Tetrahedron Lett.* **2011**, *52*, 4957.
29. Choudary, B. M.; Ranganath, K. V. S.; Yadav, J.; Kantam, M. L. *Tetrahedron Lett.* **2005**, *46*, 1369.
30. Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167.
31. Baharfar, R.; Baghbanian, S. M.; Vahdat, S. M. *Tetrahedron Lett.* **2011**, *52*, 6018.
32. Baharfar, R.; Porahmad, N. *Phosphorus, Sulfur Silicon Relat. Elem*. **2011**, *186*, 1988.
33. Baharfar, R.; Vahdat, S. M.; Hakimabadi, F. G. *Monatsh. Chem.* **2009**, *140*, 489.

