ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 4, pp. 837–841. © Pleiades Publishing, Ltd., 2017.

An Efficient Reduction of Nitro and Bromine Naphthalene Derivatives[1]

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Received January 11, 2017

Abstract—Reduction of 1,5-dimethoxy-4-nitronaphthalene by hydrazine hydrate was optimized in the course of current study. Influence of metals, temperature and solvents upon the process was tested. Yield of the reaction was the highest in the presence of Zn powder in DMF. Moderate heating made the process slightly more efficient than that at room temperature, whereas high temperature led to a decreased yield. The current approach made it possible to exclude high pressure and diminish experimental costs.

Keywords: nitro naphthalenes, reduction, naphthylamines, hydrazine hydrate, zinc powder

DOI: 10.1134/S1070363217040272

INTRODUCTION

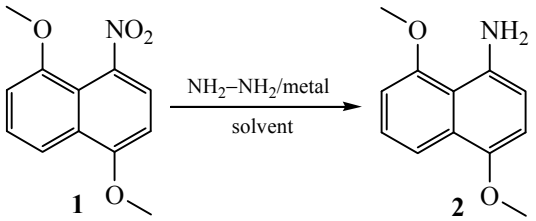
Naphthylamines are valuable building blocks and act as intermediates in synthesis of various pharmaceuticals. For example, *N*-aryl-naphthylamines interfere the interaction between HIV integrase and the cofactor LEDGF/p75 [1]. As potent antiaggregating βA agents, *N*-arylnaphthylamines were used in treating the Alzheimer disease and other neurological diseases caused by deposits of amyloid aggregates [2]. Naphthylamines are widely used in preparation of fluorescent probes [3, 4]. Reduction of nitro compounds was considered to be one of the prevailing approaches to amines. In most cases reduction of nitro compounds involves high pressure catalytic hydrogenation in the presence of a metal in acidic aqueous or organic media [5]. Palladium, platinum, and rhodium complexes [6–9] are used as catalysts. Naphthylamines are usually obtained by reduction of the corresponding nitronaphthalenes in the presence of H_2 and Pd or Pb and hydrochloric acid. Such approaches are characterized by some limitations including high pressure, application of extensive palladium catalysts, health risks [3], complicated work up, and some more. In the current study we present an efficient method of preparing naphthylamines by using hydrazine hydrate in the presence of metals under optimized temperature and media.

RESULTS AND DISCUSSION

Reduction of 1,5-dimethoxy-4-nitronaphthalene **1** by H_2 with Pd or Sn was used as the model processes that led to yields of 57% and 39% respectively [12]. Such low efficiency of the process stimulated our search for a more efficient method. Hydrazine hydrate is a conventional powerful reducing agent that can react with nitro compounds in the presence of Pd or Ni to give the corresponding amino compounds [11, 12]. The current study was carried out with various metal reducing agents, solvents and temperatures pursuing low cost and high efficiency. Reduction of compound **1** was carried out with a variety of activated powdered metals, Mg, Al, Zn, Fe, and Sn, in MeOH at ambient temperature. $SnCl_2$ and CuCl were also tested in the process (see the table). Zn powder demonstrated the highest efficiency (yield 84%). No target compounds were detected among the products formed in the presence of Sn, Cu and CuCl powders or hydrazine hydrate at room temperature. Al, Mg and Fe powders exhibited the activity similar to that of Pd/C–H_2 leading to 4,8-dimethoxy-1-naphthylamine with the yields of 52, 61, and 63%, respectively. Interestingly, all of the studied metals, except $SnCl_2$, demonstrated no significant difference in affecting the reaction time at room temperature. The process was monitored by TLC that indicated no by-products formation upon prolonged the reaction time. Though $SnCl_2$ could shorten reaction time with the yield of 71%, the following work-up was complicated because of poor solubility of $SnCl_2$ in water and generation of by-products. The reaction with NH_2–NH_2/Zn at ambient temperature (entries 11–14) proceeded smoothly in MeOH, DCM, THF, or DMF with substantial yields. The highest yield (94%) was achieved in DMF. Upon

[1] The text was submitted by the authors in English.

Reduction of 1,5-dimethoxy-4-nitronaphthalene under various reaction conditions



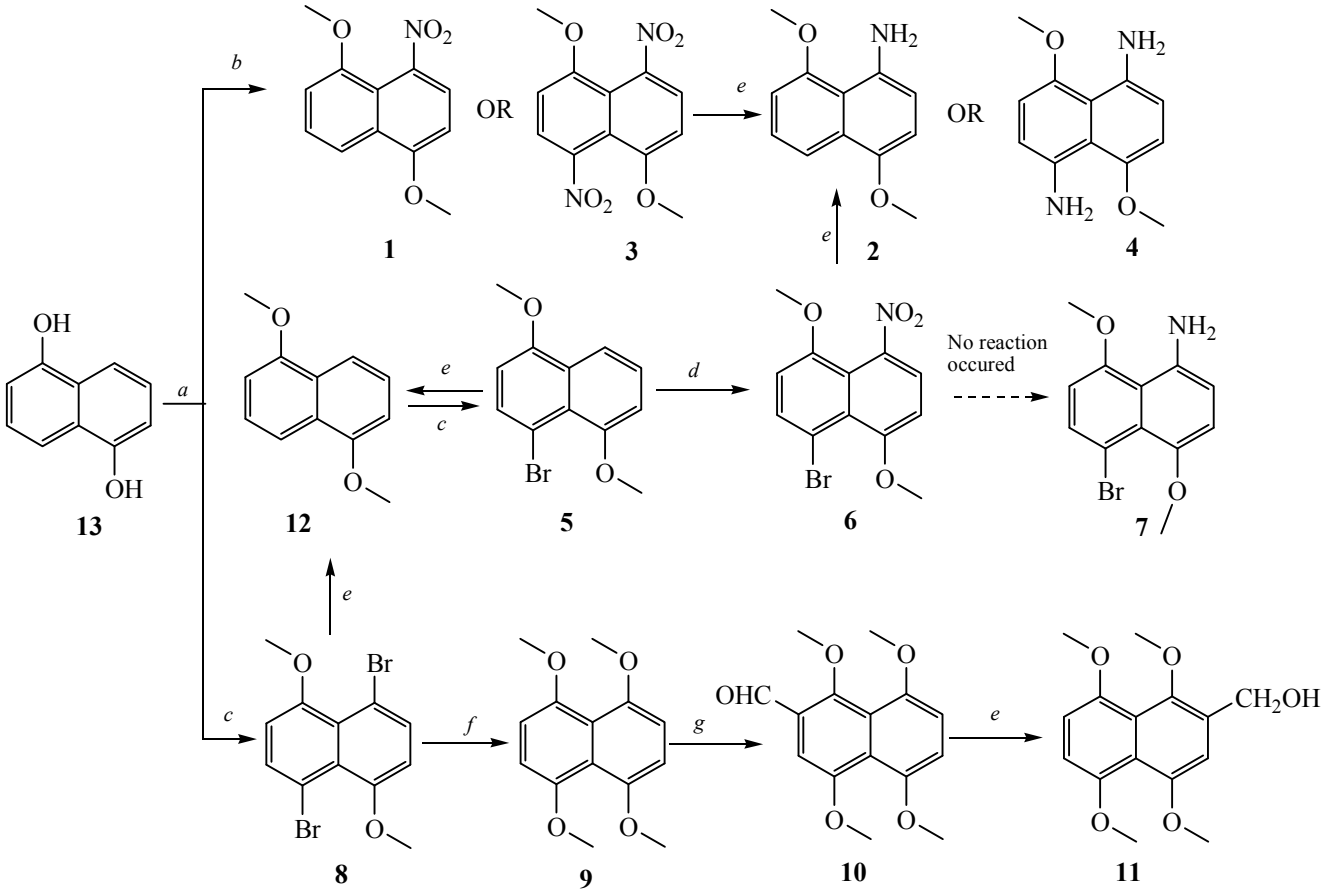
Entry no.	Reducing agent	Solvent	*T*, °C	Time, h	Yield, %[a]
1	Pd/C–H_2	MeOH	Room temperature	12	57
2	Sn	HCl–MeOH	Reflux	3	39
3	NH_2–NH_2	MeOH	Room temperature	24	0
4	NH_2–NH_2/Al	MeOH	Room temperature	30	52
5	NH_2–NH_2/Mg	MeOH	Room temperature	30	61
6	NH_2–NH_2/Fe	MeOH	Room temperature	24	63
7	NH_2–NH_2/Sn	MeOH	Room temperature	24	0
8	NH_2–NH_2/$SnCl_2$	MeOH	Room temperature	1	71
9	NH_2–NH_2/Cu	MeOH	Room temperature	24	0
10	NH_2–NH_2/CuCl	MeOH	Room temperature	24	0
11	NH_2–NH_2/Zn	MeOH	Room temperature	36	84
12	NH_2–NH_2/Zn	DCM	Room temperature	16	72
13	NH_2–NH_2/Zn	THF	Room temperature	36	54
14	NH_2–NH_2/Zn	DMF	Room temperature	36	90
15	NH_2–NH_2/Zn	DMF	50	12	91
16	NH_2–NH_2/Zn	DMF	100	8	76

[a] Isolated yields.

completion of the process Zn powder was filtered off and a pale white crude product **2** could be used as a reactant directly without further purification. Heating of the reaction mixture at 50°C made the process slightly more efficient than that at room temperature (yields of 91% and 90%, respectively), and high temperature (100°C) led to decreased yield (76%).

Based on the preliminary data, NH_2–NH_2/Zn induced reduction of 1,5-dimethoxy-4,8-dinitronaphthalene **3**, 1-bromo-4,8-dimethoxy-5-nitronaphthalene **6** and 1,4,5,8-tetramethoxy-2-naphthaldehyde **10** in DMF at 50°C was subsequently carried out for determining the scope and limitations of the reducing system. 1,5-Dimethoxynaphthalene **12** served as the key intermediate in the synthesis (Scheme 1) which was easily prepared from 1,5-dihydroxynaphthalene **13** by the process of methylation. Formation of mononitro or dinitro derivatives **1** and **3** could be controlled by the amount of nitric acid. Similarly, bromine containing compounds **5** and **8** were synthesized by addition of the corresponding amounts of NBS. Aldehyde **10** was prepared on the basis of our earlier study [13]. Dinitro compound **3** could be efficiently reduced under the optimized conditions into 4,8-dimethoxynaphthalene-1,5-diamine **4** with high yield (87%) without any 4,8-dimethoxy-5-nitronaphthalen-1-amine formed. Under similar conditions the compound **6** gave the product of its debromination **2** (83%) instead of the expected compound **7**. Tendency to debromination was tested also with intermediates **5** and **8**. The product **12** was obtained in high yield via reducing both compounds. Such result suggested a promising method of dehalogenation in organic synthesis. Reduction of compound **10** induced by NH_2–NH_2/Zn proceeded over longer period of time and led to the corresponding product **11** (yield 71%). In general, the reducing system under study could be used with various compounds, though with some limitations. The probable mechanisms of reduction of nitro and

Scheme 1.



a: $(CH_3)_2SO_4$, NaOH, THF–H_2O, 0°C; *b*: HNO_3, HOAc, room temperature; *c*: NBS, CH_3CN, room temperature; *d*: HNO_3, HOAc, 0°C; *e*: NH_2-NH_2/Zn, DMF, 50°C; *f*: CH_3ONa, DMF–CH_3OH, reflux; *g*: $POCl_3$, DMF, DCM, reflux.

bromine compounds as well as aldehydes is presented in Scheme 2.

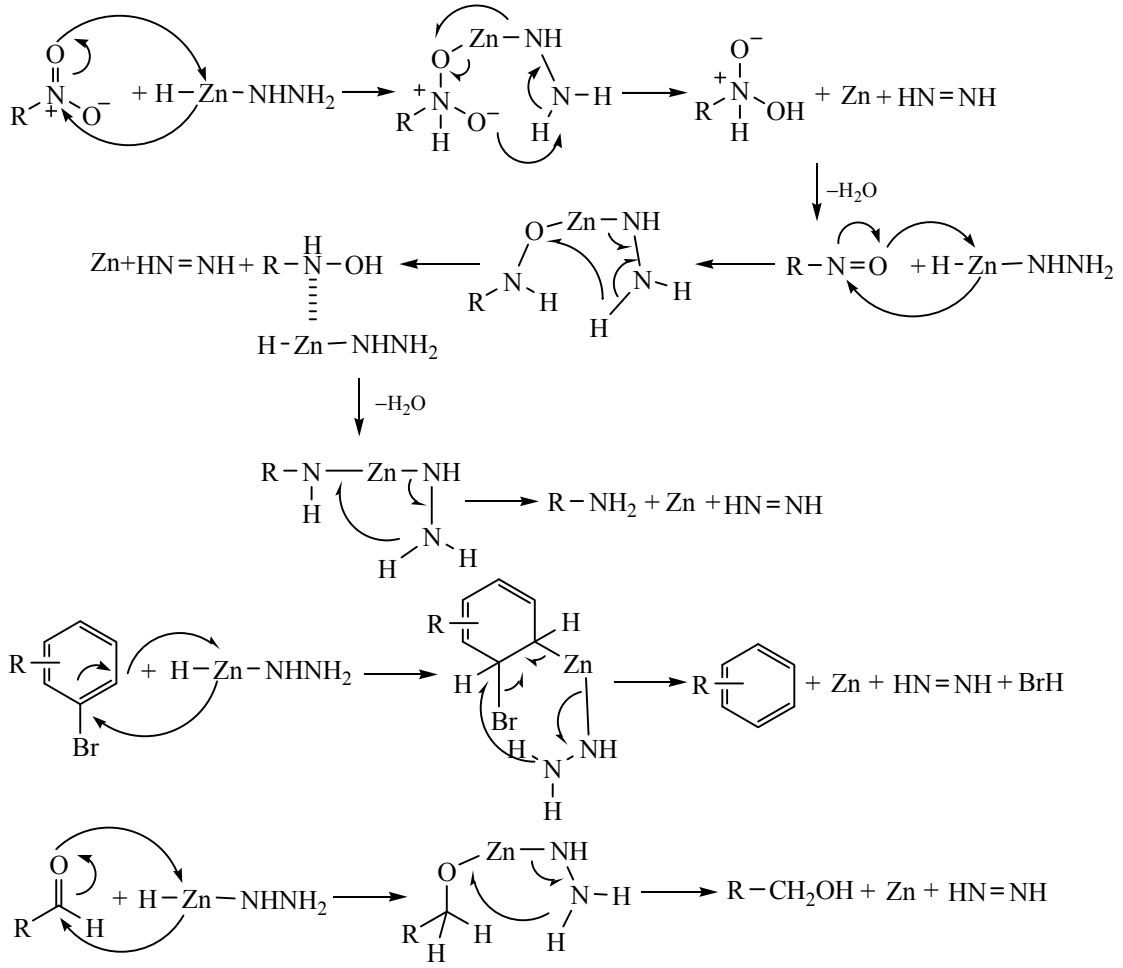
EXPERIMENTAL

Chemicals and solvents were purchased from commercial suppliers. All anhydrous solvents were purified and dried according to standard methods. NMR spectra were measured on a Varian Mercury-300 (400 MHz) spectrometer in DMSO-d_6 using TMS as the standard. Reactions progress was monitored by TLC (silica gel GF_{254}) and visualized with UV light (254 nm). Some products were purified by flash chromatography (silica gel 100-200 mesh). Metal powders were activated by pretreating with HCl (1M) and washing with water and ether thoroughly.

1,5-Dimethoxy-4-nitronaphthalene (1). 70% Nitric acid (1.5 mL) in acetic acid (1.5 mL) was added slowly to a stirred suspension of 1,5-dimethoxy-naphthalene (3.76 g, 20 mmol) in acetic acid (50 mL) at room temperature. Upon stirring overnight at ambient temperature, the precipitate was filtered off and washed with water. The crude product was recrystallized from methanol and dried. Light yellow solid, yield 85%. ^{1}H NMR spectrum, δ, ppm: 3.92 s (3H), 4.03 s (3H), 6.74 d (J = 8.3 Hz, 1H), 7.01 d (J = 7.8 Hz, 1H), 7.44–7.53 m (2H), 7.90 d (J = 8.5 Hz, 1H). ^{13}C NMR spectrum, δ, ppm: 56.03, 56.06, 102.24, 108.31, 114.68, 117.16, 121.65, 127.15, 127.21, 141.18, 153.64, 157.04.

4,8-Dimethoxy-1-naphthylamine (2). To a stirred suspension of 1,5-dimethoxy-4-nitronaphthalene (1.2 g, 5 mmol) and activated Zn powder (1.3 g, 20 mmol) in DMF (20 mL) was added 85% hydrazine hydrate (1.2 g, 20 mmol) at 50°C under the atmosphere of N_2. Upon completion of the reaction (TLC), Zn powder was filtered off and the filtrate was poured into ice

Scheme 2. Plausible mechanisms for reduction of nitro, bromine and formyl derivatives by NH_2–NH_2/Zn.



R = alkyl or aryl.

water (500 mL). The crude product was precipitated, filtered off and purified by column chromatography on silica gel. White solid, yield 91%. ^{1}H NMR spectrum, δ, ppm: 3.81 s (3H), 3.90 s (3H), 5.68 s (2H), 6.48 d (J = 8.3 Hz, 1H), 6.76 d (J = 8.3 Hz, 1H), 6.82 d (J = 7.7 Hz, 1H), 7.27 t (J = 8.1 Hz, 1H), 7.59 d (J = 8.5 Hz, 1H). ^{13}C NMR spectrum, δ, ppm: 56.03, 56.16, 104.81, 107.60, 107.89, 114.46, 115.20, 125.56, 127.92, 139.83, 145.44, 157.85.

1,5-Dimethoxy-4,8-dinitronaphthalene (3). 70% Nitric acid (4.5 mL) in acetic acid (4.5 mL) was added slowly to a stirred suspension of 1,5-dimethoxy-naphthalene (3.76 g, 20 mmol) in acetic acid (50 mL) at room temperature. Upon stirring overnight at ambient temperature, the precipitate was filtered off, washed with water, recrystallized from methanol, and dried. Light yellow solid, yield 82%. ^{1}H NMR spectrum, δ, ppm: 3.91 s (6H), 7.31 d (J = 8.5 Hz, 2H), 8.01 d (J = 8.5 Hz, 2H). ^{13}C NMR spectrum, δ, ppm: 57.45, 107.87, 116.85, 124.51, 140.69, 155.01.

4,8-Dimethoxynaphthalene-1,5-diamine (4). To a stirred suspension of 1,5-dimethoxy-4,8-dinitronaphthalene (1.4 g, 5 mmol) and activated Zn powder (1.3 g, 20 mmol) in DMF (20 mL) was added 85% hydrazine hydrate (1.2 g, 20 mmol) at 50°C under the atmosphere of N_2. The following procedure was carried out the same way as presented above for the product **2**. Yield 87%. ^{1}H NMR spectrum, δ, ppm: 3.71 s (6H), 5.61 s (4H), 6.36 d (J = 8.4 Hz, 2H), 6.60 d (J = 8.4 Hz, 2H). ^{13}C NMR spectrum, δ, ppm: 57.21, 108.33, 108.41, 117.15, 140.21, 148.33.

1-Bromo-4,8-dimethoxynaphthalene (5). To a suspension of 1,5-dimethoxy-naphthalene (3.76 g, 20 mmol) in acetonitrile (50 mL) was added NBS (3.9 g, 22 mmol) at room temperature. Upon stirring for 2 h, the precipitate was filtered off and washed with

acetonitrile thus giving the crude product which was recrystallized from methanol and dried. Cyan-blue solid, yield 88%. ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H), 3.90 s (3H), 6.74–7.13 m (2H), 7.29-7.48 m (1H), 7.54–7.87 m (2H). ^{13}C NMR spectrum, δ, ppm: 55.51, 55.72, 105.05, 107.99, 108.26, 114.92, 125.94, 128.76, 132.23, 133.67, 154.69, 155.48.

1-Bromo-4,8-dimethoxy-5-nitronaphthalene (6). 70% Nitric acid (1.5 mL) in acetic acid (1.5 mL) was added slowly to a stirred suspension of 1-bromo-4,8-dimethoxynaphthalene (5.3 g, 20 mmol) in acetic acid (50 mL) and the mixture was stirred for at 0°C. Upon completion of the process (TLC) the precipitate was filtered off, washed with water and purified by column chromatography to give an off-white solid, yield 48%. ^{1}H NMR spectrum, δ, ppm: 3.80 s (3H), 3.93 s (3H), 7.03–7.14 m (2H), 7.73–7.91 m (2H). ^{13}C NMR spectrum, δ, ppm: 55.70, 56.27, 104.82, 107.00, 107.61, 108.26, 108.73, 122.61, 133.66, 134.59, 153.03, 157.36.

(1,4,5,8-Tetramethoxy-2-naphthyl)methanol (11). To a stirred suspension of 1,4,5,8-tetramethoxy-2-naphthaldehyde (1.4 g, 5 mmol) and activated Zn powder (1.3 g, 20 mmol) in DMF (20 mL) was added 85% hydrazine hydrate (1.2 g, 20 mmol) at 50°C under the atmosphere of N_2. Upon completion of the reaction (TLC), Zn powder was filtered off. The filtrate was poured into ice water (500 mL) and the product extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography. Yield 71%. ^{1}H NMR spectrum, δ, ppm: 3.58 s (3H), 3.70 s (3H), 3.74 s (3H), 3.80 s (3H), 5.24 s (1H), 5.27–5.41 m (2H), 6.69–6.90 m (3H). ^{13}C NMR spectrum, δ, ppm: 56.92, 57.37, 57.41, 62.49, 70.54, 108.04, 108.61, 108.97, 119.53, 122.19, 133.82, 146.36, 150.03, 151.33, 152.32.

CONCLUSIONS

An efficient synthetic method for reduction of nitronaphthalene derivatives by using commercial hydrazine hydrate and Zn powder is reported. Besides the nitro group, it can be suitable for bromo and formyl groups. DMF was determined to be the most appropriate solvent. Mild heating could accelerate the reaction. Contrary to the earlier methods, the current approach is characterized by decreased experimental cost and no pressure equipment involved. Probably the method can be extended to reducing some polycyclic nitro and bromine compounds.

ACKNOWLEDGMENTS

The study was supported by Shanghai Science and Technology Innovation Program (no. 15431900700), Shanghai Natural Science Fund (no. 16ZR1418100) and China Postdoctoral Science Foundation (no. 2014M561479).

REFERENCES

1. Crucitti, G.C., Pescatori, L., Messore, A., Madia, V.N., Pupo, G., Saccoliti, F., Scipione, L., Tortorella, S., Di Leva, F.S., Cosconati, S., Novellino, E., Debyser, Z., Christ, F., Costi, R., and Santo, R.D., *Eur. J. Med. Chem.*, 2015, vol. 101, p. 288. doi 10.1016/j.ejmech.2015.06.036
2. Di Santo, R., Costi, R., Cuzzucoli Crucitti, G., Pescatori, L., Rosi, F., Scipione, L., Celona, D., Vertechy, M., Ghirardi, O., Piovesan, P., Marzi, M., Caccia, S.,Guiso, G., Giorgi, F., and Minetti, P., *J. Med. Chem.*, 2012, vol. 55, no. 19, p. 8538. doi 10.1021/jm301105m
3. Sun, S., Qiao, B., Jiang, N., Wang, J., Zhang, S., and Peng, X., *Org. Lett.*, 2014, vol. 16, no. 4, p. 1132. doi:10.1021/ol500284p
4. Brito, R.M. and Vaz, W.L., *Anal. Biochem.*, 1986, vol. 152, no. 2, p. 250. doi 10.1016/0003-2697(86)90406-9
5. Orlov, V.Y., Begunov, R., Demidova, N.Y., and Rusakov, A., *Russ. J. Gen. Chem.,* 2006, vol. 76, no. 1, p. 76. doi 10.1134/S1070363206010154.
6. Li, Z., Li, J., Liu, J., Zhao, Z., Xia, C., and and Li, F., *ChemCatChem*, 2014, vol. 6, no. 5, p. 1333. doi 10.1002/cctc.201301037
7. Du, W., Chen, G., Nie, R., Li, Y., and Hou, Z., *Catal. Commun.*, 2013, vol. 41, p. 56. doi 10.1016/j.catcom.2013.06.038
8. Cai, S., Duan, H., Rong, H., Wang, D., Li, L., He, W., and Li, Y., *ACS Catal.*, 2013, vol. 3, no. 4, p. 608. doi 10.1021/cs300689w
9. Islam, S., Tuhina, K., Mubarak, M., and Mondal, P., *J. Mol. Catal. A: Chem.*, 2009, vol. 297, no. 1, p. 18. doi 10.1016/j.molcata.2008.09.010
10. Serin, S., *Transit. Metal. Chem.*, 2001, vol. 26, no. 3, p. 300. doi 10.1023/A:1007163418687
11. King, L. C., Kohan, M. J., Brooks, L., Nelson, G. B., Ross, J. A., Allison, J., Adams, L., Desai, D., Amin, S., and Padgett, W., *Chem. Res. Toxicol.*, 2001, vol. 14, no. 6, p. 661. doi 10.1021/tx0001373
12. Thomson, R., Race, E., and Rowe, F., *J. Chem. Soc. (Resumed)*, 1947, p. 350.
13. Wang, R., Zheng, X., Zhou, W., Peng, Y., Zhu, M., and Li, S., *J. Chem. Res.* 2010, vol. 34, no. 9, p. 520. doi 10.3184/030823410X12843836823191