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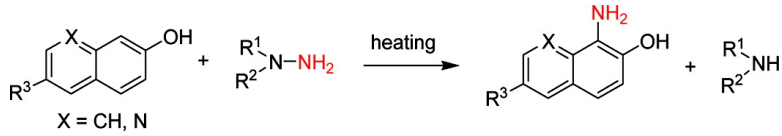


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# A New Method for N−N Bond Cleavage of N,N-Disubstituted Hydrazines to Secondary Amines and Direct Ortho Amination of Naphthol and Its Analogues

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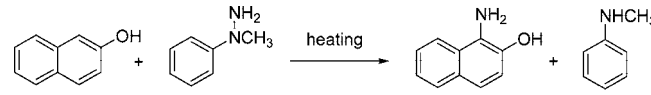
N−N bond cleavage in hydrazines occupies a significant place in chemistry for the synthesis of amines[1] which are important pharmacophores in numerous biologically active compounds and have been greatly touted in the area of drug discovery.[2] Developing efficient and general preparative methods for secondary amines from N,N-disubstituted hydrazines is of promising interest. On the other hand, the ortho-aminated derivatives of naphthol and its analogues have a broad range of applications in preparation of dyes,[3] pharmaceuticals,[4] and so on. Traditionally, ortho-aminated naphthol and its analogues are prepared by nitration and subsequent reduction,[4b,d,5] reduction of azo-compounds,[6] which often suffer from harsh conditions and limited generality. Direct ortho amination, which is superior to traditional methods at least with respect to synthetic steps, is quite rare. A thorough search of the literature revealed a single report of α-amination reaction of 2-naphthol with *N,N*-dimethylhydrazine under radical reaction conditions: sodium methoxide and oxygen atmosphere as well as irradiation with a tungsten lamp.[7] It was especially pointed out that no aminated product could be detected under argon. The substrates were limited to 2-naphthol, *N,N*-dimethyl-, and *N,N*-diethylhydrazine.[7]

This Communication describes an unexpected reaction of N,N-disubstituted hydrazines with naphthol and its analogues under simply thermal conditions that leads to a general and efficient method for the N−N bond cleavage of N,N-disubstituted hydrazines and direct ortho amination of naphthol and its analogues.

The reaction of naphthol with hydrazines usually results in the substitution of the phenolic hydroxyl group of naphthol by hydrazine residue, and then followed by benzidine rearrangement to produce the corresponding 2,2′-diamino-1,1′-biaryls or carbazoles in the case of arylhydrazines.[8] To our surprise, however, when we heated a mixture of 2-naphthol with *N*-methyl-*N*-phenylhydrazine at 80 °C under argon atmosphere, we obtained the unexpected α-aminated product 1-amino-2-naphthol and *N*-methylaniline (Scheme 1).

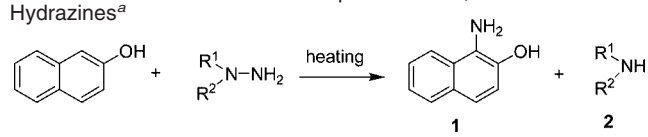
A preliminary study was performed to determine the substrate scope of this reaction. To our delight, not only *N*-alkyl-*N*-arylhydrazines (Table 1, entries 1−6), but other types of *N,N*-disubstituted hydrazines, *N,N*-diarylhydrazine (Table 1, entry 7), *N,N*-dialkylhydrazines (Table 1, entries 8 and 9) also reacted smoothly with 2-naphthol under argon to afford 1-amino-2-naphthol and the corresponding secondary amines in good to excellent yields. The reaction was typically performed at a temperature slightly higher than that of where the reactants mixture melted.[9] However, in the case of *N*-benzyl-*N*-phenylhydrazine and *N,N*-diphenylhydrazine, the reaction did not occur at a temperature lower than 100 °C (Table 1, entries 3 and 7).

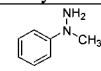
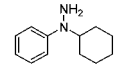
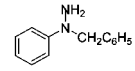
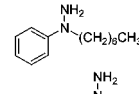
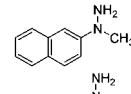
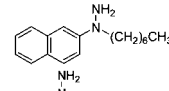
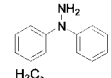
***Scheme 1***[a]




[a] Reaction conditions: 1:1 substrate molar ratio, 80 °C, argon atmosphere.

***Table 1.*** Reaction Results of 2-Naphthol with N,N-Disubstitued Hydrazines[a]



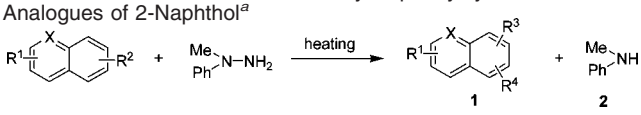

| Entry | *N,N*-Disubstituted hydrazine | T (°C) | Yield (%)[b] 1 | 2 |
|---|---|---|---|---|
| 1 |  | 80 | 94 (35[d]) | 95 (88[d]) |
| 2 |  | 90 | 93 (33[d]) | 96 (79[d]) |
| 3 |  | 120 | 85 | 92 |
| 4 |  | 90 | 94 | 95 |
| 5 |  | 90 | 93 | 95 |
| 6 |  | 90 | 93 | 95 |
| 7 |  | 120 | 91 | 95 |
| 8[c] |  | 80 | 91 (11[d]) | –[e] |
| 9 |  | 80 | 65 | 70 |

[a] Reaction conditions: 1:1 molar ratio of 2-naphthol to hydrazine, argon atmosphere. [b] Isolated yields. [c] Reaction run using 2 equiv of hydrazine. [d] Reaction was carried out in methanol at 20 °C. [e] The yield was not measured.

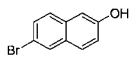
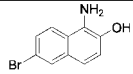
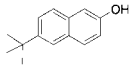
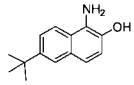
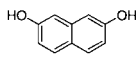
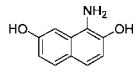
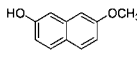
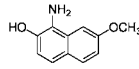
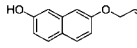
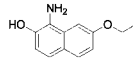
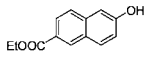
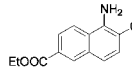
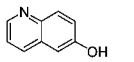
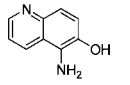
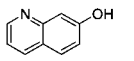
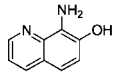
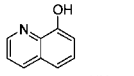
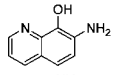
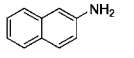
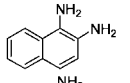
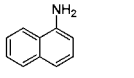
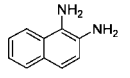
*N,N*-Dimethylhydrazine reacted cleanly under argon and thermal conditions to afford 1-amino-2-naphthol in 91% yield (Table 1, entry 8). The yield of gaseous dimethylamine was not determined. The reaction of *N,N*-diisobutylhydrazine was more complex judged from TLC, thus offered moderate yields of the desired products (Table 1, entry 9). *N*-Acyl-*N*-arylhydrazines such as *N*-acetyl-*N*-phenylhydrazine and *N*-benzoyl-*N*-phenylhydrazine were also examined, but we did not detect any α-aminated product even at a higher temperature.


10.1021/ja711153b CCC: $40.75 

***Table 2.*** Reaction Results of *N*-Methyl-*N*-phenylhydrazine with Analogues of 2-Naphthol[a]




**1** **2**

| Entry | Substrate | T (°C) | Product **1** | Yield (%) [b] **1** | **2** |
|---|---|---|---|---|---|
| 1 |  | 90 |  | 94 | 95 |
| 2 |  | 90 |  | 93 | 95 |
| 3[c] |  | 130 |  | 93 | 93 |
| 4 |  | 90 |  | 92 | 94 |
| 5 |  | 90 |  | 92 | 95 |
| 6 |  | 90 |  | 91 | 94 |
| 7[c] |  | 130 |  | 58 | 89 |
| 8[c] |  | 130 |  | 45 | 88 |
| 9 |  | 90 |  | 31 | 71 |
| 10 |  | 90 |  | 40 | 56 |
| 11 |  | 90 |  | 10 | 36 |

[a] Reaction conditions: 1:1 substrate molar ratio, argon atmosphere. [b] Isolated yields. [c] Reaction was carried out in chlorobenzene.

The reaction could also be carried out in solvent. For example, *N*-methyl-*N*-phenylhydrazine, *N*-cyclohexyl-*N*-phenylhydrazine, *N,N*-dimethylhydrazine reacted with 2-naphthol in methanol at 20 °C under argon in a longer reaction time (15, 15, and 60 h, respectively) to afford products in lower yields (Table 1, entries 1, 2, and 8).

To further evaluate the scope of this reaction, a variety of analogues of naphthol were employed. Like 2-naphthol, 6-bromo-2-naphthol, 6-*tert*-butyl-2-naphthol, 2,7-naphthalenediol, 7-methoxy-2-naphthol, 7-allyloxy-2-naphthol, and ethyl 6-hydroxy-2-naphthoate reacted readily with *N*-methyl-*N*-phenylhydrazine and exhibited high yields (Table 2, entries 1−6). It is noted that only one amino group was introduced onto 2,7-naphthalenediol. This may be attributed to the steric hindrance rising from the amino group that is already situated at C-1. The same reason may explain why 8-acetamino-2-naphthol did not react with *N*-methyl-*N*-phenylhydrazine under similar conditions. The reactions of 2,7-naphthalenediol, 6-hydroxyquinoline, and 7-hydroxyquinoline were performed in chlorobenzene because of their high melting points. The reactions of 6-, 7-, and 8-hydroxyquinoline with *N*-methyl-*N*-phenylhydrazine gave the corresponding aminated hydroxyquinolines in moderate yields (Table 2, entries 7−9). Interestingly, although 1-naphthol did not give the ortho-aminated product 2-amino-1-naphthol, 8-hydroxyquinoline produced 7-amino-8-hydroxyquinoline in about 30% yield (Table 2, entry 9). 2-Naphthalenamine could also be ortho aminated by this method giving naphthalene-1,2-diamine in 40% yield (Table 2, entry 10). In the case of 1-naphthalenamine, only 10% of the ortho-aminated product was attained (Table 2, entry 11). Monocyclic phenols and arylamines, such as phenol, 4-methylphenol, 4-methoxyphenol, 4-nitrophenol, aniline, and *N*-methylaniline did not undergo this reaction.

In summary, an unexpected reaction of *N,N*-disubstituted hydrazine with naphthol and its analogues under simply thermal conditions has been disclosed. This finding provides a new general approach to the cleavage of N−N bond of N,N-disubstituted hydrazines, which can be used for the synthesis of secondary amines. The direct ortho amination of naphthol and its analogues, which is advantageous over traditional synthesis, may find its wide application in preparation of many valuable organic compounds. Further work will focus on the reaction mechanism, the reactions of structurally more complex hydroxyl- and amino-substituted arenes, as well as the utilization of this reaction in the syntheses of complex molecules.

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**Supporting Information Available:** Experimental procedures and spectroscopic characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Selected examples for N−N bond cleavage in hydrazines: Hinman, R. L. *J. Org. Chem.* **1957**, *22*, 148–150. (b) Feuer, H.; Brown, F., Jr. *J. Org. Chem.* **1970**, *35*, 1468–1471. (c) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219–6223. (d) Alonso, F.; Radivoy, G.; Yus, M. *Tetrahedron* **2000**, *56*, 8673–8678. (e) Fernandez, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2893–2897. (f) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491–4493. (g) Enders, D.; Funabiki, K. *Org. Lett.* **2001**, *3*, 1575–1577. (h) Ding, H.; Frestad, G. K. *Org. Lett.* **2004**, *6*, 637–640. (i) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 897–900. (j) Sinha, P.; Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 3741–3744.
(2) (a) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811. (b) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166–4176.
(3) Fabian, J.; Nakazumi, H.; Matsuoka, M. *Chem. Rew.* **1992**, *92*, 1197–1226.
(4) (a) Israel, M.; Zoll, E. C. *J. Org. Chem.* **1972**, *37*, 3566–3567. (b) Musser, J. H.; Jones, H.; Sciortino, S.; Bailey, K.; Coutts, S. M.; Khandwala, A.; Sonnino, G. P.; Leibowitz, M.; Wolf, P.; Neiss, E. S. *J. Med. Chem.* **1985**, *28*, 1255–1259. (c) Sleath, P. R.; Noar, J. B.; Eberlein, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 3328–3338. (d) Maryanoff, B. E.; Nortey, S. O.; McNally, J. J.; Sanfilippo, P. J.; McComsey, D. F.; Dubinsky, B.; Shank, R. P.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1547–1552.
(5) Giorgini, E.; Petrucci, R.; Astolfi, P.; Mason, R.-P.; Greci, L. *Eur. J. Org. Chem.* **2002**, 4011–4017.
(6) Bin, D. L.; Lindley, J. M.; Meth, C. O. *Synthesis* **1978**, 23–24.
(7) Barton, D. H. R.; Greneur, S. L.; Motherwell, W. B. *Tetrahedron. Lett.* **1983**, *24*, 1601–1604.
(8) (a) Japp, F. R.; Maitland, W. *J. Chem. Soc.* **1903**, *83*, 267–276. (b) Fuchs, W.; Niszel, F. *Chem. Ber.* **1927**, *60*, 2058–2062. (c) Darke, N. L. *Organic Reactions*; Wiley: New York, 1942, *1*, 105−128. (d) Seeboth, H.; Bärwolff, D.; Becker, B. *Liebigs Ann. Chem.* **1965**, *683*, 85–92. (e) Seeboth, H.; Neumann, H.; Gïsch, H. *Liebigs Ann. Chem.* **1965**, *683*, 93–99. (f) Seeboth, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 307–317. (g) Miyano, S.; Nawa, M.; Mori, A.; Harukichi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2171–2176. (h) Brown, K. J.; Berry, M. S.; Murdoch, J. R. *J. Org. Chem.* **1985**, *50*, 4345–4349. (i) Yamamoto, Y.; Sakamoto, A.; Nishioka, T.; Oda, J.; Fukazawa, Y. *J. Org. Chem.* **1991**, *56*, 1112–1119. (j) Vyskočil, Š.; Smrčina, M.; Lorenc, M.; Tišlerová, I.; Brooks, R. D.; Kulagowski, J. J.; Langer, V.; Farrugia, L. J.; Kočovský, P. *J. Org. Chem.* **2001**, *66*, 1359–1365.
(9) Differential scanning calorimetry (DSC) tests show the reactions are slightly exothermic. See Supporting Information.

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