

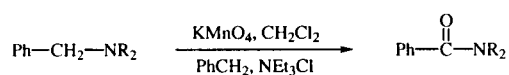
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Received January 5, 1999

The synthesis of *N*-phenyl lactams by phase transfer oxidation of *N,N*-(polymethylene) anilines with potassium permanganate is reported.

*J. Heterocyclic Chem.*, **37**, 109 (2000).

The conversion of tertiary amines to amides under conditions of phase transfer catalysis was first reported two decades ago, but was limited to the oxidation of substituted dihydro 1,2,3-triazoles by potassium permanganate [1]. Shortly afterwards a new reagent, benzyltriethylammonium permanganate, was shown to effect the same type of oxidation for an extensive series of amines, including seven tertiary amines [2]. Although reaction was regiospecific in only two cases with *N,N*-dialkylanilines, the principal difficulty was the extreme instability of the reagent [3].

Recently, we reported a safe and convenient method for the oxidation of tertiary benzylamines to benzamides by potassium permanganate with phase transfer catalysis [4].



By analogy to the similar oxidation of benzyl ethers [5], the reaction is considered to proceed *via* a benzylic carbocation, which is stabilized by both the adjacent phenyl and amino groups. When R was methyl and/or ethyl, regiospecificity was not observed. The amount of benzamide, acetamide, and formamide reflected the relative stabilities of the corresponding cationic intermediates. These results, along with the products from dimethyl(2-phenylethyl)amine, established that nonbenzylic methylene groups adjacent to nitrogen can be oxidized under mild conditions. That fact led us to consider the utility of this method for nonbenzylic tertiary amines. The present report summarizes our findings.

For preparatively useful applications we focused on symmetrical *N,N*-dialkylanilines. The aniline moiety was potentially detrimental, since its ability to delocalize the nitrogen electron pair could decrease the stabilization of the intermediate carbocation. Such was not observed with benzyl-diphenylamine; but, in that case, the methylene group was benzylic [4]. We chose *N,N*-(polymethylene) anilines, since their conversion to *N*-phenyl lactams provides a new route to this class of compounds. In particular, we anticipated that 1-phenylazetidine could serve as a model precursor to 1-aryl  $\beta$ -lactams of current biological interest [6].

We initially oxidized *N,N*-diethylaniline in order to compare our phase transfer method with the direct use of benzyltriethylammonium permanganate. Although better

results (63%) were obtained with the latter reagent [2], its hazardous nature remains problematic. Our procedure afforded product in approximately 50%, which led us to examine the cyclic aniline derivatives in Table 1. The results were fair to good, and the safety and convenience of the method are advantageous. While we were unable to achieve good yields of 1-phenyl-2-azetidinone, the process is still noteworthy as the only route to  $\beta$ -lactams in which the carbonyl function is formed after ring construction [7]. With 4-phenylmorpholine (**7**) the product was exclusively 4-phenyl-3-morpholinone (**8**), reflecting the same regiospecificity observed earlier [1]. The only other reported oxidation of such systems involved manganese dioxide, but the course of the reaction was different [8].

Table 1  
Oxidation of Tertiary *N*-Phenylanilines

	Amine	Reflux Time (hours)	Yield [a] (%)	Product	
1	Ph-N(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>	1.5 3 6	49 50 51		2
3		0.8 1.5 3	60 66 (50) 61		4
5		1.5 3 6	59 67 70		6
7		1.5 3 6	42 53 48 (45)		8
9		1.5 3	84 82		10
11		2 3 15[b]	29 32 33 (25)		12

[a] Yields ( $\pm 1\%$ ) determined by gc-ms analysis; yield of isolated product in parentheses. [b] At room temperature.

## EXPERIMENTAL

## General Methods.

Starting materials and products were obtained from Aldrich Chemical Co. (**1**, **5**, **7**, **10**), received as a gift (**6**), or prepared by literature methods and purified to the reported physical and spectral properties (**2** [9], **3** [10], **9** [11], **11** [12]). Product analyses were performed on a Hewlett-Packard 5890II gas chromatograph with a SPB-5 polydiphenyl(5%)-dimethyl(95%)siloxane column (30 m x 200  $\mu$ m with 0.2  $\mu$ m film) and Hewlett-Packard 5971A mass spectrometer (EI, 70 eV). Products were identified by comparison with authentic compounds. Product yields ( $\pm 1\%$ ) for duplicate runs were measured with 2,3-dimethylnaphthalene as internal standard and included detector calibration factors for each compound. Proton nmr spectra were recorded at 300 MHz in deuteriochloroform on a Bruker DPX 300 spectrometer; chemical shifts are reported in parts per million ( $\delta$ ) relative to tetramethylsilane. Infrared spectra were obtained as potassium bromide pellets on a Nicolet 550 FT-IR spectrophotometer. Melting points (uncorrected) were determined on a modified Hershberg apparatus with matched Anschutz thermometers.

Oxidation of *N,N*-Dialkylanilines: Analytical Procedure.

To a stirred solution of the amine (1.00 mmole) and benzyltriethylammonium chloride (0.683 g, 3.00 mmoles) in dichloromethane (10 ml) was added finely ground potassium permanganate (0.474 g, 3.00 mmoles), and the purple solution was stirred at reflux for the times specified in Table 1. The mixture was cooled in an ice bath and a solution of sodium bisulfite (2 g) in water (10 ml) was added slowly with vigorous stirring, which was continued until the color was completely discharged. The biphasic mixture was diluted with water (10 ml) and separated; the aqueous phase was extracted with chloroform (3 x 10 ml). The combined organic extract was washed with water (20 ml), dried (anhydrous sodium sulfate), filtered into a 50-ml volumetric flask containing 2,3-dimethylnaphthalene (0.156 g, 1.00 mmole), and the flask was filled to the mark with chloroform. An aliquot (1 ml) was diluted similarly (to 25 ml) and analyzed by gas chromatography/mass spectrometry.

Hexahydro-1-phenyl-2*H*-azepin-2-one (**4**).

Oxidation of **3** (0.350 g, 2.00 mmoles) was carried out by the above procedure for 1.5 hours. Removal of the solvent gave a residual orange liquid, which was chromatographed on alumina with hexane/chloroform (4:1) as eluant to give crude **4** as a yellow solid (0.190 g, 50%); mp 65-68°. Purification by flash chromatography on silica gel with hexane/ethyl acetate (1:1) as eluant afforded **4** as white crystals; mp 71.5-72°, lit mp 72-72.5° [14], ir 1655  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr  $\delta$  1.83 (m, 6H; H-4,5,6), 2.70 (m, 2H; H-3), 3.75 (m, 2H; H-7), 7.19-7.40 (m, 5H; phenyl).

4-Phenyl-3-morpholinone (**8**).

Oxidation of **7** (0.326 g, 2.00 mmoles) was carried out by the above procedure for 6 hours. Removal of the solvent gave a residual yellow solid (0.275 g, 75% **8** by gc-ms), which was recrystallized from hexane to give **8** as white crystals (0.159 g, 45%); mp 112-113°, lit mp 110-111° [13]; ir 1655  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr  $\delta$  3.77 (t, 2H, J = 5.0 Hz; H-5), 4.04 (t, 2H, J = 5.1 Hz; H-6), 4.35 (s, 2H; H-2), 7.26-7.45 (m, 5H; phenyl).

1-Phenyl-2-azetidinone (**12**).

Oxidation of **11** (0.400 g, 3.00 mmoles) was carried out by the above procedure at room temperature for 15 hours. Removal of the solvent gave a residual pale yellow solid, which was chromatographed on silica gel with hexane/ethyl acetate as eluant to give **12** as white crystals (0.110 g, 25%); mp 79.2-79.7°, lit mp 78-79° [15]; ir 1737  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  nmr  $\delta$  3.12 (t, 2H, J = 1.7 Hz; H-3), 3.63 (t, 2H, J = 1.7 Hz; H-4), 7.06-7.38 (m, 5H; phenyl).

## Acknowledgments.

We are grateful to Dr. Peter M. Wege II for a summer stipend (C.A.S.) and the Williams College Faculty Research Fund for financial support. We thank Prof. E.-C. Wang (Kaohsiung Medical College, Taiwan) for the sample and spectra of **6** and Dr. D. M. T. Chan (DuPont Agricultural Products, Newark, DE) for the spectra of **4**.

## REFERENCES AND NOTES

- [1] L. M. Rossi and P. Trimarco, *Synthesis*, 743 (1978).
- [2] H.-J. Schmidt and H.J. Schäfer, *Angew. Chem. Int. Ed. Engl.*, **20**, 109 (1981).
- [3a] H. Jäger, J. Lütolf and M. W. Meyer, *Angew. Chem. Int. Ed. Engl.*, **18**, 786 (1979); [b] H.-J. Schmidt and H. J. Schäfer, *Angew. Chem. Int. Ed. Engl.*, **18**, 787 (1979); [c] J. Graefe and R. Rienäcker, *Angew. Chem. Int. Ed. Engl.*, **22**, 625 (1983).
- [4] J. H. Markgraf, P. K. Sangani and M. Finkelstein, *Synth. Commun.*, **27**, 1285 (1997).
- [5] K. N. Rankin, Q. Liu, J. Hendry, H. Yee, N. A. Noureldin and D. G. Lee, *Tetrahedron Letters*, **39**, 1095 (1998).
- [6a] J. W. Clader, D. A. Burnett, M. A. Caplen, M. S. Domalski, S. Dugar, W. Vaccaro, R. Sher, M. E. Browne, H. Zhao, R. E. Burrier, B. Salisbury and H. R. Davis, Jr., *J. Med. Chem.*, **39**, 3684 (1996); [b] L.-Y. Chen, A. Zaks, S. Chackalamannil and S. Dugar, *J. Org. Chem.*, **61**, 8341 (1996); [c] M. J. Meegan, C. M. Waldron, R. D. Keaveny and A. D. Neary, *J. Chem. Res. (S)*, 158 (1997); [d] C. Kashima, K. Fukusaka and K. Takahashi, *J. Heterocyclic Chem.*, **34**, 1559 (1997); [e] M. Shimizu, S. Maruyama, Y. Suzuki and T. Fujisawa, *Heterocycles*, **45**, 1883 (1997); [f] B. K. Banik, M. S. Manhas and A. K. Bose, *Tetrahedron Letters*, **39**, 5077 (1997); [g] G. Wu and W. Tormos, *J. Org. Chem.*, **62**, 6412 (1997); [h] A. Abouabdellah, J.-P. Bégué, D. Bonnet-Delpon and T. T. Nga, *J. Org. Chem.*, **62**, 8826 (1997); [i] B. Alcaide, A. Rodríguez-Vicente and M. A. Sierra, *Tetrahedron Letters*, **39**, 163 (1998); [j] B. A. McKittrick, K. Ma, K. Huie, N. Yumibe, H. Davis, Jr., J. W. Clader, M. Czarniecki and A. T. McPhail, *J. Med. Chem.*, **41**, 752 (1998); [k] S. Matsui, Y. Hashimoto and K. Saigo, *Synthesis*, 1161 (1998); [l] V. Molteni, R. Annunziata, M. Cinquini, F. Cozzi and M. Benaglia, *Tetrahedron Letters*, **39**, 1257 (1998); [m] B. Alcaide and A. Rodríguez-Vicente, *Tetrahedron Letters*, **39**, 6589 (1998).
- [7] L. Ghosez and J. Marchand-Brynaert, *Comprehensive Organic Synthesis*, **5**, 90 (1991).
- [8] H. B. Henbest and A. Thomas, *J. Chem. Soc.*, 3032 (1957).
- [9a] R. A. W. Johnstone and M. E. Rose, *Tetrahedron*, **35**, 2169 (1979); [b] R. Brehme, *Synthesis*, 113 (1976).
- [10] R. E. Walkup and S. Searles, Jr., *Tetrahedron*, **41**, 101 (1985).
- [11a] J. A. Clark and J. M. Miller, *J. Am. Chem. Soc.*, **99**, 498 (1977); [b] L. C. Craig and R. M. Hixon, *J. Am. Chem. Soc.*, **52**, 804 (1930).
- [12a] L. W. Deady, G. J. Leary, R. D. Topsom and J. Vaughan, *J. Org. Chem.*, **28**, 511 (1963); [b] R. Bird, A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1215 (1973).
- [13] S. R. Tulyaganov and Z. Seitkasymov, *Zh. Org. Khim.*, **6**, 1305 (1970); *Chem. Abstr.*, **73**, 66523m (1970).
- [14] D. M. T. Chan, *Tetrahedron Letters*, **37**, 9013 (1996).
- [15] T. Okawara, T. Matsuda and M. Furukawa, *Chem. Pharm. Bull.*, **30**, 1225 (1982).