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Novel synthesis of dibenzo[*b*,*g*]1,5-oxazocines

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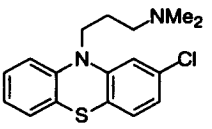
Abstract

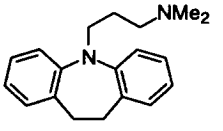
An efficient approach to dibenzo[*b*,*g*]1,5-oxazocines on solid support is described. The procedure is based on the intramolecular nucleophilic aromatic substitution of fluorine from the derivatives of 2-fluoro-5-nitrobenzaldehyde with the OH function of immobilized phenols. Good yields, and excellent purities of the targeted heterocycles are the advantages of the reported procedure.

Keywords: supported reagents; supported reactions; aza compounds.

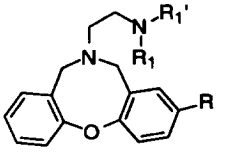
The tricyclic aza-heterocyclic systems are of current interest to medicinal chemists due to their pronounced activity as strong central nervous system suppressants and anticancer agents. Selected examples of these compounds are presented below.



Chloropromazine



Imipramine



Dibenzo[b,g]1,5-oxazocines

Chloropromazine and imipramine are well-known agents currently used for the treatment of depression. Derivatives of these compounds have also been efficacious in other therapeutic areas including arteriosclerosis, Parkinson's disease, and various cancers.[1] Related heterocycles of the dibenzo[*b*,*g*]1,5-oxazocine series were also reported to possess CNS activities, and used for the treatment of pain and/or inflammation.[2] Two main strategies have been devised to synthesize the dibenzo[*b*,*g*]1,5-oxazocine core. One approach involves the reaction of the dibromide **A** with primary amines to afford the desired oxazocines **B**.[3] The alternative path proceeds through bromination of the biphenyl ether **C** followed by treatment with potassium phthalimide, hydrazinolysis of the resultant intermediate, and subsequent intramolecular cyclization of the amine to afford the targeted eight-membered lactam **D**.[3]

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† This paper is dedicated with respect and admiration to my Teacher, Dr. Victor V. Semenov on the occasion of his 50th birthday.

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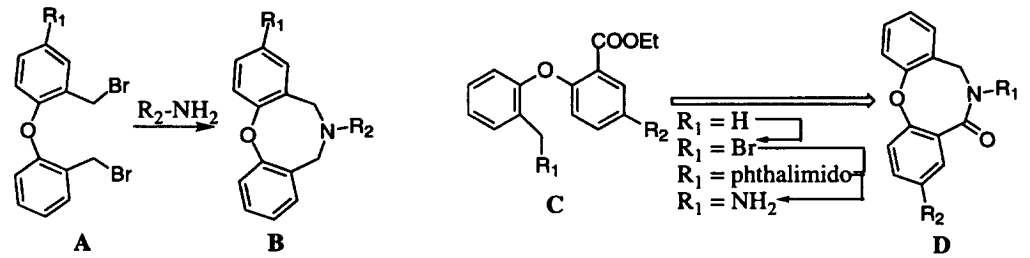
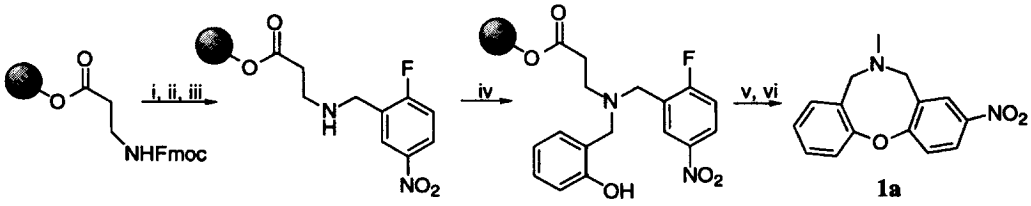


The disadvantages of these reported procedures are: (i) they are both multistep syntheses; and (ii) they both result in formation of the side products. In order to bypass these disadvantages we decided to assemble the dibenzo[*b*,*g*]1,5-oxazocine core via the nucleophilic aromatic substitution (S_NAr)[4] of fluorine with the phenolic OH function of the properly assembled noncyclic precursor (Scheme 1).



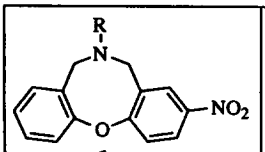
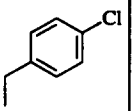
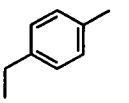
Scheme 1. (i) 20% piperidine, DMF, rt, 20 min; (ii) 2-fluoro-5-nitrobenzaldehyde (**1**), TMOF, 12 h; (iii) $NaBH(OAc)_3$, AcOH (1%), DMF, 8 h; (iv) salicylic aldehyde (**A**), $NaBH(OAc)_3$, AcOH (1%), DMF, 8 h; (v) 5% DBU/DMF, 24 h; (vi) MeI (**a**), DMF, 12 h; Hunig's base, DCM, 1 h

Some examples of this strategy include the elegant synthesis of vancomycin and the related macrocyclic antibiotics,[5] as well as the parallel synthesis of dibenzo[*b*,*f*]oxazepines.[6] Application of solid support allowed us to synthesize a diverse array of the desired heterocycles, as well as to avoid the purification steps.

β-Alanine immobilized on Wang resin was selected as the solid support for this synthesis. In the optimized procedure,[7] reductive amination of the β-alanine resin with 2-fluoro-5-nitrobenzaldehyde and $NaBH(OAc)_3$ in DMF in the presence of 1% TFA took place smoothly to afford the desired secondary amine. The second reductive amination with salicylic aldehyde afforded the expected tertiary amine in a 64% yield (determined by TFA cleavage). The intermediate was treated with 5% DBU in DMF to afford the desired immobilized nitro dibenz[*b*,*f*]oxazocine. Treatment of the resin with an array of alkyl halides in DMF followed by Hunig's base afforded the desired eight-membered heterocyles in 38–53% yield (Table 1).

General procedure for the synthesis of 3-nitro-5*H*,7*H*-dibenz[*b*,*g*]1,5-oxazocines: In a typical experimental procedure the deprotected β-Ala Wang (100 g, 0.32 mmol/g loading) resin was treated with a mixture of trimethyl orthoformate (480 mL), glacial AcOH (20 mL), and 2-fluoro-5-nitrobenzaldehyde (43 g, 250 mmol). The slurry was gently stirred under nitrogen for 8 h. The resulting immobilized imine of 2-fluoro-5-nitrobenzaldehyde was treated with a solution of $NaBH(OAc)_3$ (106 g, 500 mmol) and 5 mL of glacial acetic acid in 500 mL of anhydrous DMF. The slurry was gently stirred under nitrogen for another 12 h. In the next step, the resin was filtered, washed twice with MeOH, DCM, DMF, dioxane and Et_2O, and treated with a mixture of salicylaldehyde (31 g, 250 mmol) and $NaBH(OAc)_3$ (106 g, 500 mmol) in 500 mL of anhydrous DMF for an additional 12 h. The resin was filtered, washed twice with MeOH, DCM, DMF, dioxane and Et_2O, and dried in vacuo to afford, the precursor for the intramolecular cyclization. The resultant resin (100 mg) was shaken with 100 mL of a 5% solution of DBU in DMF at room temperature for 24 h, filtered, and treated with 10% AcOH in DMF to remove excess DBU. The resin was then washed with DMF, MeOH, CH_2Cl_2, and dried in vacuo. The resulting

Table 1
Yields[a] and purities of nitro dibenzo[*b*,*g*]1,5-oxazocines

 1	Me a	 b	 c	 d	 e
Yield, %	52	50	38	49	53
HPLC purity, %	>99	96	98	99	98
Retention time, min[b]	3.75	4.53	5.32	5.82	5.68

[a]The yields are for unpurified compounds.
[b]The column employed was an Ultrasphere C18 cartridge 250mm x 4.6 mm. The solvent system was MeCN/H_2O (start: 5:95 ratio; finish: 10:90; 8 min runs; .1% TFA added), with a flow rate of 1 mL/min.

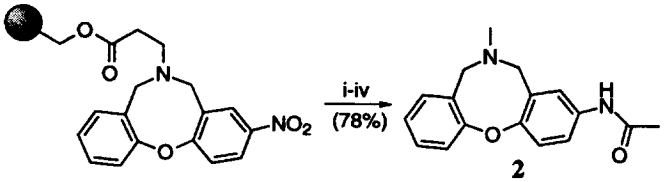
resin was treated with a 1 M solution of methyl iodide (1 mL) in DMF for 24 h, filtered, and washed with MeOH, CH_2Cl_2, and DMF. The resultant quaternized amine on solid support was treated with 5% *N*,*N*-diisopropylethylamine in CH_2Cl_2 (100 mL) for 12 h. The filtrate was collected, and washed twice with a saturated $NaHCO_3$ solution. The extract was dried over $MgSO_4$, filtered and coevaporated twice with MeOH to afford the desired products as pale yellow solids.[8]

In summary we have described an efficient synthesis of dibenzo[*b*,*g*]1,5-oxazocines on solid support. The procedure is based on the intramolecular nucleophilic aromatic substitution of fluorine from the derivatives of 2-fluoro-5-nitrobenzaldehyde with the OH function of immobilized phenols. Good yields and excellent purities of the targeted heterocycles are the advantages of the procedure.[9]

References

1. (a) Mueller, A. L.; Moe, S. T. US Patent 1997, 873011; (b) Vermeulin, N. M. J.; O'Day, C. L.; Webb, H. K.; Burns, M. R.; Bergstrom, D. E. US Patent 1998, 85538; (c) Averback, P.; Ghanbari, H.; Beheshti, I.; Morse, D. US Patent 1997, 858343; (d) Haddjeri, N.; Blier, P.; De Montigny, C. *J. Neurosci.* **1998**, *18*, 10150; (e) Kuo, C. *Biophys. J.* **1998**, *75*, 2845; (f) Ocharan, M. E.; Asbun, J.; Valencia, I.; Castillo, C.; Castillo, E. F. *Proc. West. Pharmacol. Soc.* **1998**, *41*, 141; Gallego, M.; Casis, L.; Casis, O. *Eur. J. Pharmacol.* **1998**, *360*; (g) Jagadeesh, S. R.; Subhash, M. N. *Biol. Psychiatry* **1998**, *44*, 617; (h) Adali, O.; Carver, G. C.; Philpot, R. M. *Arch. Biochem. Biophys.* **1998**, *358*, 92; (i) Casis, O.; Sanchez-Chapula, J. A. *J. Cardiovasc. Pharmacol.* **1998**, *32*, 521; (j) Zhu, J.; Mix, E.; Bengtsson, B.-O.; Link, H. *J. Peripher. Nerv. Syst.* **1997**, *2*, 30; (k) Muraoka, S.; Kamei, K.; Muneoka, K.; Takigawa, M. *J. Neurochem.* **1998**, *71*, 1709; (l) Boyer, P.-A.; Skolnick, P.; Fossom, L. H. *J. Mol. Neurosci.* **1998**, *10*, 219; (m) Wuonola, M.; Palfreyman, M. G.; Motohashi, N.; Kawase, M.; Gabay, S.; Gupta, R. R.; Molnar, J. *Anticancer Res.* **1998**, *18*, 337; (n) Pajeva, I.; Wiese, M. *J. Med. Chem.* **1998**, *41*, 1815.
2. (a) Joergensen, T. K.; Andersen, K. E.; Andersen, H. S.; Hohlweg, R.; Madsen, P.; Olsen, U. B. Dutch Patent 96-DK 138 960401; CA 1996, 713004; (b) Ohgoh, T.; Tanaka, S.; Fujimoto, M.; Kitahara, A. *Yakugaku Zassi* **1977**, *97*, 24; (c) Gellatly, R. P.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1976**, 913; (d) Tanaka, S.; Hashimoto, K. *Yakugaku Zassi* **1973**, *93*, 1003.
3. (a) Tanaka, S.; Hashimoto, K. Japan Patent JP 690908; CA 1972, 59680; (b) Tanaka, S.; Hashimoto, K.; Watanabe, H.; Sakaguchi, K. *Chem. Pharm. Bull.* **1973**, *21*, 1683; (c) Tanaka, S.; Hashimoto, K. US Patent 1974, 3,803,143; (d) Lieb, F.; Eiter, K. *Liebigs Ann. Chem.* **1976**, *14*, 203; (e) Tanaka, S.; Ogata, Y. *Yakugaku Zassi* **1972**, *93*, 1003.

4. For selected publications on S_NAr see, for example: (a) Terrier, F. *Nucleophilic Aromatic Displacement: The Role of the Nitro Group*; VCH: New York, 1991, Chapter 1; (b) Artamkina, G. A.; Egorov, M. P.; Beletskaya, I. P. *Chem. Rev.* **1982**, *82*, 427.
5. (a) Boger, D. L.; Yohannes, D.; Zhou, J.; Patane, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 3420; (b) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem.* **1997**, *62*, 4721; (c) Zhu, J. *Synlett* **1997**, 133 and references cited therein; (d) Gonzalez, G. I.; Zhu, J. P. *J. Org. Chem.* **1997**, *62*, 7544; (e) Evans, D. A.; Barrow, J. C.; Watson, P. S.; Ratz, A. M.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M.; Ellman, J. A.; Rychnowsky, S. D.; Lacour, J. *J. Am. Chem. Soc.* **1997**, *119*, 3419; (f) Evans, D. A.; Dinsmore, C. J.; Ratz, A. M.; Evrard, D. A.; Barrow, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 3417; (g) Kiselyov, A. S.; Eisenberg, S.; Luo, Y. *Tetrahedron* **1998**, *54*, 10635; (h) Kiselyov, A. S.; Eisenberg, S.; Luo, Y. *Tetrahedron Lett.* **1999**, *40*, 2465.
6. Ouyang, X.; Tamayo, N.; Kiselyov, A. S. *Tetrahedron* **1999**, *55*, 2827.
7. Initially, we attempted the reductive amination reaction of salicylaldehyde A and immobilized β-alanine (0.32 mmol/g loading) in DMF in the presence of 1% AcOH. However, treatment of the resin with 20% TFA in CH_2Cl_2 afforded the expected amino acid in only a 7% yield. Additionally, attempts to conduct a second reductive amination of the resultant resin with 2-fluoro-5-nitrobenzaldehyde were unsuccessful under a variety of experimental conditions. However, changing the reductive amination sequence proved to be successful.
8. Selected analytical data: yields are based on the initial 0.32 mmol/g loading of β-alanine resin. 6-Methyl-3-nitro-5*H*,7*H*-dibenzo[*b*,*g*]1,5-oxazocine (**1a**). Yield: 5 mg (52%); m.p. 99–101°C. IR (KBr) ν: 1517s, 1477s, 1337, 1274, 1253 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.09 (dd, J_1=9.0 Hz, J_2=3.0 Hz, 1H), 7.59 (d, J=3.0 Hz, 1H), 7.29–7.15 (m, 5H), 4.70–3.50 (m, 4H), 2.20–1.80 (m, 3H); ^{13}C NMR (DMSO-d_6) 133.2, 131.5, 131.1, 130.4, 130.1, 128.1, 125.7, 124.7, 124.6, 123.3, 122.3, 121.0, 120.6, 120.4, 59.8, 42.8, 37.6; HRMS (FAB) calcd for $C_{15}H_{14}N_2O_3$: m/z=271.1083 (MH^+), found: 271.1081.
9. The synthesized library of dibenzo[*b*,*f*]1,5-oxazocines can be further transformed into the corresponding amides via the previously reported procedure.[6]



2

Reagents and Conditions: i) $SnCl_2$ H_2O, 1.5M in DMF, RT, 8 h; ii) Ac_2O, Hunig's base CH_2Cl_2, RT, 8h; iii) MeI, DMF, 12 h; iv) Hunig's base, DCM, 1 h

N-(6-Methyl-5*H*,7*H*-benzo[*b*]benzo[3,4-*g*]1,5-oxazocine-3-yl)acetamide (**2**). Yield: 7.0 mg (78%); m.p. 57–58°C t_R=0.67 min (100% pure); IR (KBr) ν: 3095m, 1682s, 1619s, 1350s cm^{-1}; ^1H NMR (CD_2Cl_2): δ 7.54 (s, 1H), 7.37 (dd, J_1=9 Hz, J_2=3.0 Hz, 1H), 7.23–7.21 (m, 3H), 7.06–6.98 (m, 2H), 4.6 (br s, 1H), 3.54 (br s, 3H), 2.30–1.80 (m, 6H); ^{13}C NMR (CD_2Cl_2) 169.3, 135.7, 133.0, 132.9, 132.8, 129.8, 125.2, 123.8, 123.0, 121.4, 120.4, 120.0, 60.1, 42.2, 37.3, 24.5; HRMS (FAB) calcd for $C_{17}H_{18}N_2O_2$: m/z=283.1447 (MH^+), found: 283.1445.