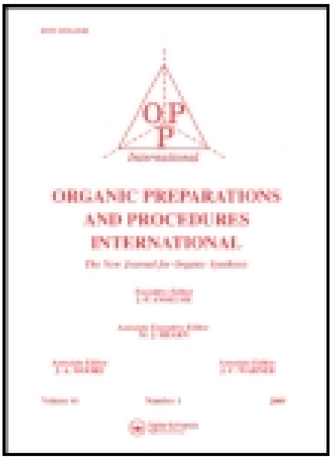


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

A Practical Synthesis of 5,5′-Methylene-bis(benzotriazole)

Haining Gu [b] , Biao Yu [a] , Peng-Fei Zhang [a] & Wei-Ming Xu [b]

[a] College of Material, Chemistry and Chemical Engineering , Hangzhou Normal University , Hangzhou, PR, China

[b] Analytical Center , Zhejiang University , Hangzhou, PR, China

Published online: 22 Apr 2009.

Organic Preparations and Procedures International, 41:162–164, 2009

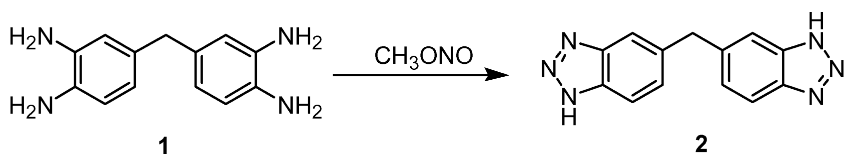
ISSN: 0030-4948 print
DOI: 10.1080/00304940902802172

A Practical Synthesis of 5,5′-Methylene-*bis*(benzotriazole)

Haining Gu,[2] Biao Yu,[1] Peng-Fei Zhang,[1] and Wei-Ming Xu[2]

[1]College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou, P. R. China
[2]Analytical Center, Zhejiang University, Hangzhou, P. R. China

5,5′-Methylene-*bis*(benzotriazole) (**2**) is a versatile intermediate in the preparation of several metal passivators[1] and light-sensitive materials.[2] Though it is a useful molecule, a review of the literature, including patents, indicated the absence of an easily performed synthesis. As part of our research program on the study of green chemistry,[3] we have developed a practical pilot-scale method for the preparation of 5,5′-methylene- *bis*(benzotriazole) from methyl nitrite and tetraaminodiphenylmethane (*Scheme 1*). The latter compound was prepared by reduction of 3,3′-dinitro-4,4′-diaminodiphenylmethane obtained by acid-catalyzed rearrangement of *bis*(2-nitroanilino)methane according to literature procedures.[4,5] This process is efficient, environmentally benign, and easy to work up.



Scheme 1

We initially followed the conditions used by Viswanathan *et al.*[6] for the preparation of benzotriazole, but only obtained very poor yield of 5,5′-methylene-*bis*(benzotriazole) (**2**) and at least three recrystallizations were required to purify the product. Further investigation indicated that the choice of the diazotizing agent is the key factor in the above reaction and the yield of 5,5′-methylene-*bis*(benzotriazole) (**2**) increased to 92% when methyl nitrite was used instead of sodium nitrite. An outstanding feature of this process is that the purity of the crude product is greater than 98.5%.

Submitted September 26, 2008.
Address correspondence to Wei-Ming Xu, Zhejiang University, Analytical Center, Hangzhou 310028, P. R. China. E-mail: wmxu@zju.edu.cn

Experimental Section

Mps and bps are uncorrected. The purity of products was established on an Agilent 1100 HPLC. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker 400 (400 MHz) instrument with TMS as an internal standard. Infrared spectra were obtained on a Shimadzu IR-408 instrument. All chemicals were reagent grade and available commercially. The elemental analysis was performed on a Flash EA1112 instrument.

Methyl Nitrite (prepared just prior to use)

In a 1-L round-bottomed flask, fitted with a pressure equalizing addition funnel filled with 250 mL 12 M hydrochloric acid, and a gas tube in a well ventilated hood, was placed 172.5 g (2.5 mol) of sodium nitrite, 135 mL methanol, and 250 mL water. The temperature was raised to 35°C and hydrochloric acid was added dropwise over 2 hours. The methyl nitrite evolved was passed through a water trap to remove acid and then bubbled through the reaction mixture below *via* the gas tube.

5,5′-Methylene-bis*(benzotriazole)*

In a 5-L round-bottomed flask, fitted with a mechanical stirrer, and a gas tube in a well ventilated hood, was placed 270.0 g (1.18 mol) of tetraaminodiphenylmethane, 4040 mL methanol, and 440 mL of water under a nitrogen atmosphere. The temperature was raised to 40°C and methyl nitrite (152.5g, 2.5 mol, prepared above) was added through the tube for about 2 hours while the temperature was kept at about 40°C *via* water bath. When the reaction was complete, the temperature was raised to 50°C and the mixture was stirred for another 20 min. to expel excess methyl nitrite. The mixture was then poured into 7 L water, and the precipitated crystals were collected and dried *in vacuo* to afford 272.0 g (92%) of the crude product as a pale red solid (HPLC > 98.5%), mp. 238–240°C. ^{1}H NMR (DMSO-d_6): δ 4.32 (2 H, s), 7.37 (2 H, d, J = 8.8 Hz), 7.80–7.86 (4 H, m), 15.6 (2 H, b).
An analytical sample was prepared by recrystallization from methanol, mp. 239–240°C.[7]

Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.58. Found: C, 62.58; H, 3.97; N, 33.42.

Acknowledgments

We thank the National Natural Science Foundation of China (Grant No. 20602029) and the Science and Technology Foundation of Zhejiang Province (Grant No. 2007C11014) for financial support.

References

1. D. R. Clack and W. D. Philips, *GB1514359* **1978**; *Chem. Abstr.*, **89**, 215412 (1978).
2. S. Bauer, *EP268553* **1988**; *Chem. Abstr.*, **110**, 163601 (1988).
3. X. C. Yu, H. Gu and W. M. Xu, *Org. Prep. Proced. Int.*, **38**, 467 (2006).

4. N. Viswanathan, B. S. Joshi, D. H. Gawad, U. B. Gokhale, A. R. Sidhaye and G. R. Rajasekariah, *Indian J. Chem., Section B*, **24B**, 730 (1985); *Chem. Abstr.*, **105**, 172352 (1985).

5. V. V. Korshak, A. A. Izyneev, D. M. Mognonov, V. P. Mazurevskii, Zh. P. Mazurevskaya, I. S. Novak, G. F. Slezko, A. I. Prokosova and A. D. Markov, *Akad. Nauk SSSR*, 143 (1971); *Chem. Abstr.*, **78**, 110732 (1971).

6. A. A. Joshi and C. L. Viswanathan, *Bioorg. Med. Chem. Lett.*, **16**, 2613 (2006).

7. None of the previous references has reported a melting point for this compound.

Organic Preparations and Procedures International, 41:164–168, 2009

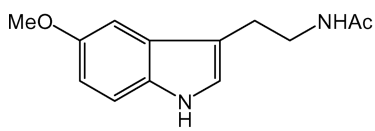
ISSN: 0030-4948 print
DOI: 10.1080/00304940902802347

A Practical Synthesis of (7-Methoxynaphth-1-yl)acetic Acid

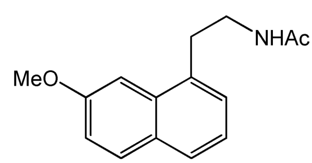
Jia-Deng Tang and Jun-Da Cen

Department of Chemistry, Shanghai Institute of Pharmaceutical Industry, Shanghai, P. R. China

The neurohormone melatonin (5-methoxy-*N*-acetyltryptamine, **1**), which is mainly secreted from the pineal gland or chemically synthesized, is putatively involved in several physiological processes including circadian rhythms, retinal physiology, seasonal breeding, and cardiovascular regulation.[1–3] Since the therapeutic efficacy of melatonin is limited by its short biological half-life, analogs of melatonin were designed and synthesized. It is known that naphthalenic ligands have a high affinity for the melatonin receptor.[4] Among these ligands, *agomelatine* (*N*-[2-(7-methoxynaphth-1-yl) ethyl]acetamide, **2**), which contains the naphthalene moiety instead of indole nucleus, is currently in clinical trial.[5]



1



2

(7-Methoxynaphth-1-yl)acetic acid (**6**), a key intermediate to **2**, has been prepared in three steps using substituted tetralone **3** as starting material[6] (*Scheme*). Treatment of **3** with $BrCH_2CO_2Et$ through a Reformatsky reaction afforded **4b** whose extranuclear double bond

Submitted July 14, 2008.
Address correspondence to Jia-Deng Tang, Department of Chemistry, Shanghai Institute of Pharmaceutical Industry, Shanghai 200437, P. R. China. E-mail: blueskytang2003@yahoo.com.cn