HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 187 - 191. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 13th June, 2013, Accepted, 8th July, 2013, Published online, 16th July, 2013
DOI: 10.3987/COM-13-S(S)31

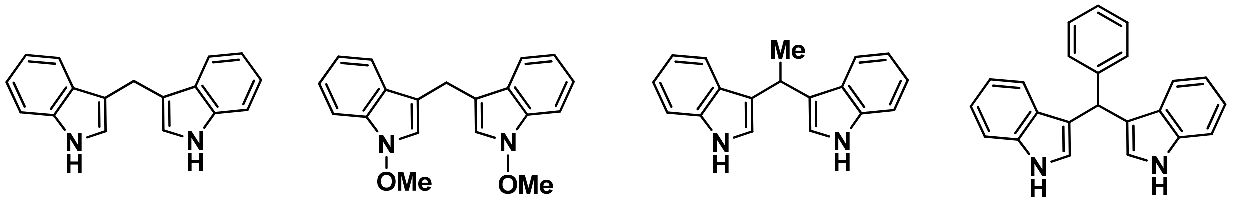
ONE-POT ACCESS TO 3,3’-BISINDOLYLMETHANES THROUGH THE INTERMOLECULAR PUMMERER REACTION

Takumi Abe, Toshiaki Ikeda, Tomoki Itoh, Noriyuki Hatae, Eiko Toyota, and Minoru Ishikura*

School of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan; E-mail: ishikura@hoku-iryo-u.ac.jp

Abstract – A one-pot synthesis of 3,3’-bisindolylmethanes was developed through the intermolecular Pummerer reaction using indole as a nucleophile.

3,3’-Bisindolylmethanes are a group of compounds with promising biological and pharmaceutical properties, such as the inhibition of cancer cell growth, and antifungal and antibacterial activities.[1] One widely used synthetic route to 3,3’-bisindolylmethane derivatives[2] (Figure 1) depends on the condensation of indoles with carbonyl compounds or their synthetic equivalents.[3] Recently, metal-catalyzed reactions have been developed for the facile synthesis of the 3,3’-bisindolylmethanes,[4] such as the Pd-catalyzed benzylic substitution of gramine with indole,[4e] and the metal-catalyzed addition of indole to allenes[4f] and alkynes.[4c] Moreover, a one-pot approach to the 3,3’-bisindolylmethanes through the Bartoli indole synthesis was developed by us.[5]



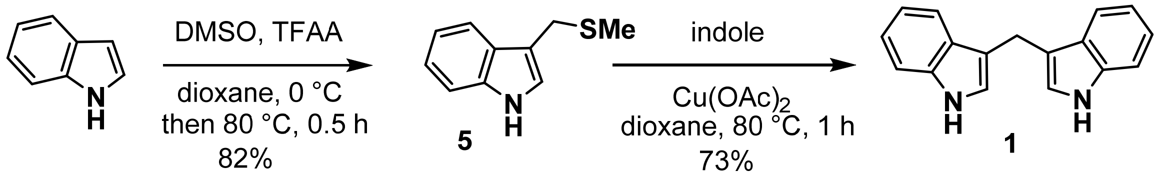
arundine (**1**) 3,3'-bis(1-methoxyindolyl)methane (**2**) vibrindole A (**3**) 3,3'-bisindolylphenylmethane (**4**)

Figure 1. 3,3’-Bisindolylmethanes

The Pummerer reaction is widely used for the synthesis of natural products and biologically interesting compounds,[6] whereas the intermolecular Pummerer reaction using indole as a nucleophile has not been extensively investigated. Recently, an intermolecular Pummerer-type reaction of indole with DMSO in the presence of $CuBr(PPh_3)_3$ and NH_4OAc was reported, although unsuitability of indole as a nucleophile under classical reaction conditions was mentioned.[7] Therefore, we have focused on developing a

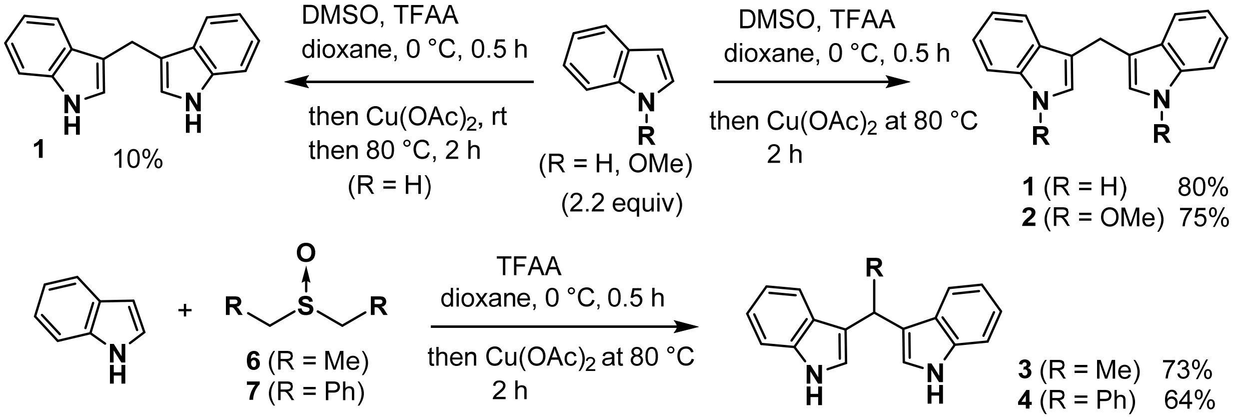
Pummerer reaction that depends on the intermolecular nucleophilic attack of indole on a sulfur-substituted carbocation intermediate. Herein, we describe a one-pot reaction for accessing 3,3'-bisindolylmethanes through the intermolecular Pummerer reaction with indole as a nucleophile.

Initially, the Pummerer reaction was attempted by adding trifluoroacetic anhydride (TFAA) to a solution of indole and DMSO in dioxane in an ice bath. This resulted in the isolation of 3-methylthiomethylindole (**5**) in only 10% yield. However, slightly changing the reaction conditions increased the yield to 82%. After treating DMSO (10 equiv) with TFAA (1 equiv) in dioxane in an ice bath for 0.5 h, the mixture was heated with indole (1 equiv) at 80 °C for 0.5 h to obtain **5**. Compound **5** was converted to arundine (**1**)[8] by heating with indole (1.2 equiv) in dioxane at 80 °C for 24 h to afford **1** in 70% yield. After several experiments, it was found that the presence of $Cu(OAc)_2$ (1 equiv) accelerated the reaction and a 73% yield was obtained by heating at 80 °C for 1 h (Scheme 1).



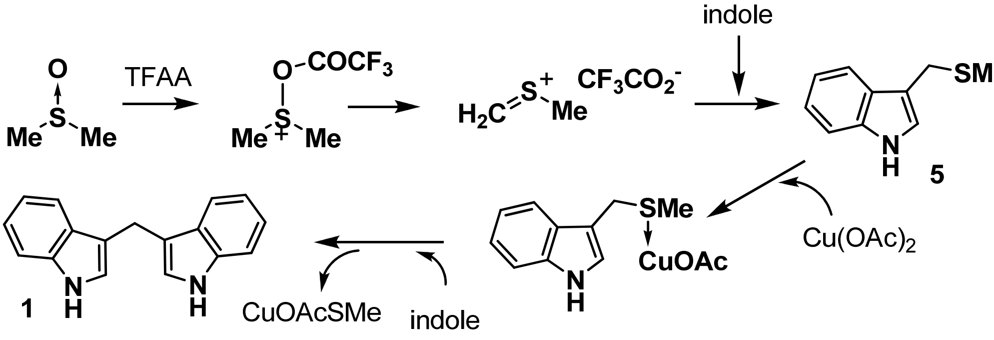
Scheme 1

These results prompted us to explore a one-pot approach for **1** (Scheme 2). Initially, TFAA (0.5 equiv) was added to a mixture of indole and DMSO (10 equiv) in dioxane in an ice bath, then the mixture was heated with $Cu(OAc)_2$ (1 equiv) at 80 °C for 2 h, but this resulted in a low yield of **1** (~10%). However, the reaction conditions were optimized and **1** was obtained in an 80% yield when $Cu(OAc)_2$ was added to the heated mixture at 80 °C.



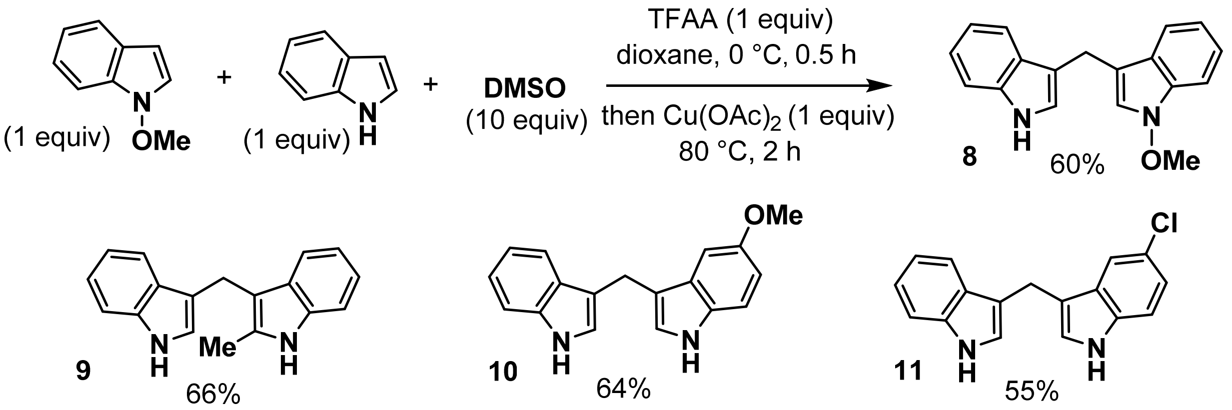
Scheme 2

Under the same conditions, 3,3’-bis(1-methoxyindolyl)methane (**2**)[9] was obtained from the reaction of *N*-methoxyindole with DMSO in 75% yield. In addition, the reaction of indole with sulfoxides **6** and **7** provided vibrindole A (**3**)[10] and 3,3’-bisindolylphenylmethane (**4**),[11] in 73 and 64% yields, respectively. A plausible reaction path is shown in Scheme 3, where **5** is activated by the interaction between the SMe group and $Cu(OAc)_2$ and undergoes a subsequent nucleophilic attack by indole (Scheme 3).



Scheme 3

Based on these results, the one-pot protocol was applied to the assembly of unsymmetric 3,3’-bisindolylmethanes using two different indoles (Scheme 4). Minor modifications were made to the protocol, and the reaction was carried out using indole and *N*-methoxyindole. After treating indole (1 equiv) with a mixture of DMSO (10 equiv) and TFAA (1 equiv) in dioxane, the mixture was heated with *N*-methoxyindole (1 equiv) at 80 °C, and then $Cu(OAc)_2$ (1 equiv) was added to the heated mixture. Additional heating for 2 h provided **8** in 60% yield. Moreover, **9** was obtained from the reaction using 2-methylindole and indole in 66% yield. The reaction of 5-methoxyindole and 5-chloroindole with indole afforded **10**[12] and **11** in 64 and 55% yields, respectively.



Scheme 4

In summary, we have developed a one-pot method for the construction of 3,3’-bisindolylmethanes by the intermolecular Pummerer reaction using indoles. Further investigation of the scope of the reaction is currently in progress.

ACKNOWLEDGEMENTS

This work was supported in part by the Ministry of Education, Culture, Sports, Sciences, and Technology of Japan through a Grant-in Aid for Scientific Research (No. 22590010 for M. I. and 23590143 for N. H.).

REFERENCES AND NOTES

1. K. R. M. Naidu, S. I. Khalivulla, S. Rasheed, S. Fakurazi, P. Arulselvan, O. Lasekan, and F. Abas, *Int. J. Mol. Sci.*, 2013, **14**, 1843; K. Abdelbaqi, N. Lack, T. Guns, L. Kotha, S. Safe, and J. T. Sanderson, *Prostate*, 2011, **71**, 1401.
2. For a review, see: M. Shiri, M. A. Zolfigol, H. G. Kruger, and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250; T. P. Pathak, J. G. Osiak, R. M. Vaden, B. E. Welm, and M. S. Sigman, *Tetrahedron*, 2012, **68**, 5203; T. Nobuta, A. Fujiya, N. Tada, T. Miura, and A. Itoh, *Synlett*, 2012, **23**, 2975.
3. R. Tayebee, M. M. Amini, F. Nehzat, O. Sadeghi, and M. Armaghan, *J. Mol. Catal. A*, 2013, **366**, 140; G. Gupta, G. Chaudhari, P. Tomar, Y. Gaikwad, R. Azad, G. Pandya, G. Waghulde, and K. Patil, *Eur. J. Chem.*, 2012, **3**, 475; S. Kamble, G. Rashinkar, A. Kumbhar, and R. Salunkhe, *Synth. Commun.*, 2012, **42**, 756.
4. (a) L. Zhang, C. Peng, D. Zhao, Y. Wang, H. J. Fu, Q. Shen, and J. X. Li, *Chem. Commun.*, 2012, **48**, 5928; (b) S. Kamble, G. Rashinkar, A. Kumbhar, and R. Salunkhe, *Synth. Commun.*, 2012, **42**, 756; (c) D. Xia, Y. Wang, Z. Du, Q. Zheng, and C. Wang, *Org. Lett.*, 2012, **14**, 588; (d) K. Ramachandiran, D. Musralidharan, and P. T. Perumal, *Tetrahedron Lett.*, 2011, **52**, 3579; (e) G. de La Herrián, A. Segura, and A. G. Csákÿ, *Org. Lett.*, 2007, **9**, 961; (f) M. P. Muñoz, M. C. de La Torre, and M. A. Sierra, *Chem. Eur. J.*, 2012, **18**, 4499.
5. T. Abe, S. Nakamura, R. Yanada, T. Choshi, S. Hibino, and M. Ishikura, *Org. Lett.*, 2013, **15**, in press.
6. S. K. Bur and A. Padwa, *Chem. Rev.*, 2004, **104**, 2401; A. Padwa and A. G. Waterson, *Curr. Org. Chem.*, 2000, **4**, 175.
7. J. Liu, X. Wang, H. Guo, X. Shi, X. Ren, and G. Huang, *Tetrahedron*, 2012, **68**, 1560.
8. B. U. Khuzhaev, S. F. Aripova, and R. S. Shakirov, *Chem. Nat. Comp.*, 1994, **30**, 635.
9. S. C. Pedras, Q. Zheng, and S. Strelkov, *J. Agric. Food Chem.*, 2008, **56**, 9949.
10. R. Bell, S. Carmeli, and N. Sar, *J. Nat. Prod.*, 1994, **57**, 1587.
11. G. A. Meshram and D. V. Patil, *Synth. Commun.*, 2010, **40**, 29; D. E. Gillespie, S. F. Brady, A. D.

Bettermann, N. P. Cianciotto, M. R. Liles, M. R. Rondon, J. Clardy, R. M. Goodman, and J. Handelsman, *Appl. Enviorn. Microbiol.*, 2002, **68**, 4301.

12. **3-(1*H*-Indol-3-ylmethyl)-5-methoxy-1*H*-indole (10):** After a mixture of TFAA (139 μL, 1 mmol) and DMSO (0.73 mL, 10 mmol) in dioxane (5 mL) was stirred at 0 °C under an argon atmosphere for 30 min, indole (117 mg, 1 mmol) was added to the mixture and the mixture was heated at 80 °C for 30 min. After cooling, 5-methoxyindole (147 mg, 1 mmol) was added to the mixture, which was then heated at 80 °C for 30 min. $Cu(OAc)_2 \cdot H_2O$ (199 mg, 1 mmol) was added next at 80 °C and the mixture was heated for 2 h. After cooling, the mixture was diluted with AcOEt (100 mL), washed with 10% aq. $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography with hexane/AcOEt (30:1) to give **10** (177 mg, 64%) as a colorless oil. IR (neat): 3408 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.81 (s, 3H), 4.21 (s, 2H), 6.86 (d, J = 8.6 Hz, 1H), 6.89 (s, 2H), 7.07 (s, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 9.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.77 (br s, 1H), 7.88 (br s, 1 H). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 56.0, 101.2, 111.2, 111.9, 112.2, 115.4, 115.7, 119.2, 119.3, 122.0, 122.3, 123.2, 127.7, 128.0, 131.7, 136.6, 153.9. HR-ESI-MS m/z: Calcd for $C_{18}H_{17}N_2O$ [$(M+H)^+$]: 277.1341. Found: 277.1345.