Efficient Synthesis of 5-(4′-Methyl[1,1′-biphenyl]-2-yl)-1*H*-tetrazole

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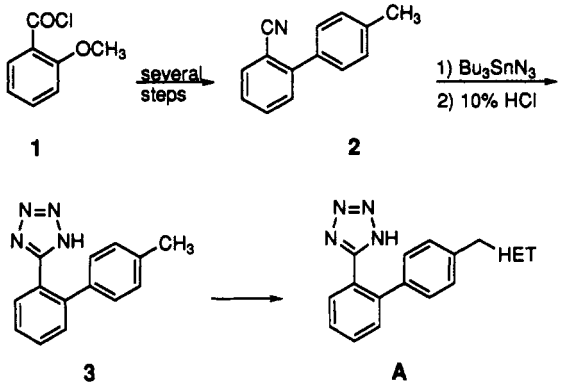
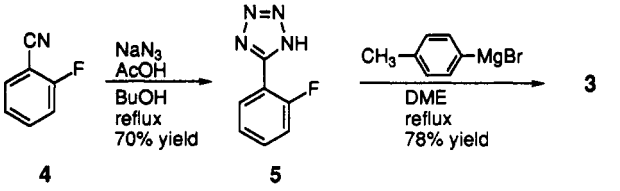
The inhibition of the renin angiotension system (RAS) has been the focus of pharmaceutical research for the last 10–12 years[1] and recently the discovery of heterocyclic agents that are angiotension II (AII) receptor antagonists[2] has produced yet another important class of potential drugs for the treatment of hypertension. Most of the reported AII inhibitors[3,4] contain the biphenylyltetrazole moiety as represented by **A**. It became clear to us from the onset of our work[4] that the only reported consistent method for the preparation of biphenylyltetrazoles was to first construct the biphenyl nitrile **2** and then convert this material to **3**.[5,6] This method has two drawbacks: (a) it requires



several steps to prepare **3** (starting with **1**) and (b) the most direct method to convert **2** to **3** requires the use of highly toxic trialkyltin azide reagents (*e.g.* tributyltin azide). In this note we report an efficient (55% overall yield) *two*-step process for the preparation of 5-(4′-methyl-[1,1′-biphenyl]-2-yl)-1*H*-tetrazole (**3**) that *avoids* the use of tin reagents and begins with the commercially available 2-fluorobenzonitrile (**4**).

The synthesis of **3** starts with the treatment of **4** with sodium azide in acetic acid/1-butanol at reflux for 2 days.[8] This phenyltetrazole is easily isolated in pure form and converted to **3** by simply treating **5** with an excess of *p*-tolylmagnesium bromide in dimethoxyethane (DME) at reflux (THF afforded very little reaction). The conversion of **5** to **3** is quantitative and allows for a simple base wash of the organic layer, followed by acidification to produce the title compound.



The use of 2-fluorobenzonitrile is key because when 2-methoxybenzonitrile is used, the tetrazole (*cf.* ref 6) can only be prepared in significant quantities by using the tin azides described above.[9] In our hands, the addition of organometallics to the (2-methoxyphenyl)tetrazole proceeded in very low yields, inpart, due to demethylation of the *o*-methoxy group. This procedure eliminates the use of toxic tin reagents, shortens the synthesis of **3** to just two steps, and represents the first example of a tetrazole-directed nucleophilic aromatic substitution reaction.

Experimental Section[10]

Preparation of 5-(2-Fluorophenyl)-1*H*-tetrazole (5). A 500-mL round-bottom flask was charged with 2-fluorobenzonitrile (48.4 g, 0.4 mol), 1-butanol (160 mL), NaN_3 (34.3 g, 0.528 mol), and glacial AcOH (31.7 g, 0.528 mol). The mixture was warmed to a mild reflux for 24 h under N_2 behind a safety shield. *CAUTION! The reaction should be carried out in a good fume hood since hydrazoic acid is explosive.* After the mixture had cooled to room temperature, it was again charged with NaN_3 (34.3 g, 0.528 mol) and AcOH (31.7 g, 0.528 mol). The mixture was warmed to reflux for an additional 24 h, cooled, and diluted with Et_2O. This organic mixture was extracted with 2 N NaOH (4 × 100 mL) and the combined ice-cold basic extract was carefully acidified to pH 1 with concentrated HCl. The product was isolated as a light gray solid (45.2 g, 68.9%) after drying under vacuum (60 °C); mp 160.5–162.0 °C (lit.[11] mp 160–162 °C). A second crop was obtained (1.0 g, 1.5%). A sample was recrystallized from H_2O to produce a white solid: mp 162.5–163.5 °C.

Preparation of 5-(4′-Methyl[1,1′-biphenyl]-2-yl)-1*H*-tetrazole (3). An ice-cold DME (1300 mL) solution of **5** (32.8 g, 0.2 mol) was slowly treated with a 1 M solution of *p*-tolylmagnesium bromide in Et_2O (Aldrich; 600 mL, 0.6 mol) under N_2. After the addition was completed, the Et_2O was removed by simple distillation and the DME solution was warmed to reflux for 16 h. With ice-bath cooling, the reaction mixture was slowly quenched with 6 N HCl (130 mL). The DME was removed under reduced pressure and the resulting aqueous residue was extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was washed with 2 N NaOH (3 × 100 mL). The combined alkaline extract was acidified to pH 1 with concentrated HCl and then extracted with

(1) Antonaccio, M. J.; Wright, J. J. Renin-Angiotensin System, Converting Enzyme, and Renin Inhibitors. In *Cardiovascular Pharmacology*; Antonaccio, M. J., Ed.; Raven Press: New York, 1990; pp 201–228.

(2) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525.

(3) For representative examples, *cf.* ref 4 and footnote 3 of ref 5.

(4) (a) Murray, W. V.; Lalan, P.; Gill, A.; Addo, M. F.; Lewis, J. M.; Lee, D. K. H.; Rampulla, R.; Wachter, M. P.; Hsi, J. D.; Underwood, D. C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1775. (b) Murray, W. V.; Lalan, P.; Gill, A.; Addo, M. F.; Lewis, J. M.; Lee, D. K. H.; Wachter, M. P.; Rampulla, R.; Underwood, D. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 369. (c) Bandurco, V. T.; Murray, W. V.; Gill, A.; Addo, M.; Lewis, J.; Wachter, M. P.; Hadden, S.; Underwood, D.; Cheung, W.-M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 375. (d) Hsi, J. D.; Murray, W. V.; Gill, A., manuscript in preparation.

(5) Duncia, J. V.; Pierce, M. E.; Santella, J. B., III *J. Org. Chem.* **1991**, *56*, 2395.

(6) A procedure was later published that starts with the commercially available 5-phenyltetrazole and employs the Suzuki coupling method[7] to prepare **3**; Lo, Y. S.; Rossano, L. T. *U.S. Patent* 5,130,439.

(7) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

(8) Similar to the procedure of Herbst, R. M.; Wilson, K. R. *J. Org. Chem.* **1957**, *22*, 1142.

(9) Trialkyltin azides are known to react more readily with electron-rich substituents, *cf.* Sisido, K.; Nabika, K.; Isida, T. *J. Organomet. Chem.* **1971**, *33*, 337.

(10) The compounds displayed the expected spectral properties and combustion analysis (±0.4% of theory).

(11) George, E. F.; Riddell, W. D. Ger. Offen. 2,310,049 (*Chem. Abstr.* **1974**, *80*, 23539y).

0022-3263/93/1958-5023$04.00/0

CH_2Cl_2. The combined extract was washed with brine and dried (Na_2SO_4) to afford 46.2 g of tan material after solvent removal. This tan material was purified by crystallization from EtOAc/hexane (2/1) to afford **3** (32.4 g, 68.6%) as a tan solid, mp 141–146 °C [lit.[5] mp 145.5–146.5° C]. The filtrate produced another 4.54 g (9.6%) of **3** after purification by silica gel filtration [CH_2Cl_2/MeOH/AcOH (97.5/2.45/0.05)]. Recrystallization from toluene (2×) afforded a tan solid, mp 144–148 °C.

Additions and Corrections

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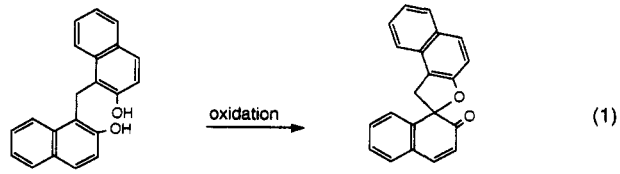
Ariel M. Litwak, Flavio Grynszpan, Oleg Aleksiuk, Shmuel Cohen, and Silvio E. Biali*. Preparation, Stereochemistry, and Reactions of the Bis(spirodienone) Derivatives of *p-tert*-Butylcalix[4]arene.

Page 394, column 1. The drawings of structures **2** and **3** in eq 1 are incorrect. The correct structures are



2 **3** (1)

We thank Professor Paris E. Georghiou (Memorial University of Newfoundland, Canada) for calling this error to our attention.