Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1769–1771
Tetrahedron Letters

Facile synthesis of 3-trimethylsilylindazoles by [3+2]cycloaddition reaction of lithium trimethylsilyldiazomethane with benzynes

Yoshimichi Shoji, Yoshiyuki Hari and Toyohiko Aoyama*

Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

Received 13 November 2003; revised 12 December 2003; accepted 12 December 2003

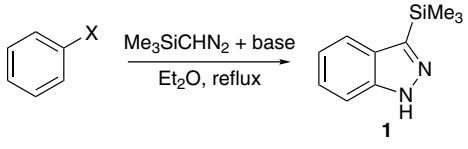
Abstract—[3+2]Cycloaddition reaction of lithium trimethylsilyldiazomethane with benzynes, generated from halobenzenes, gave the corresponding 3-trimethylsilylindazoles in good to moderate yields.

Indazole is well known as an aza analogue of indole, and a number of indazole derivatives have powerful pharmacological activities, for example, anti-inflammatory, anti-tumor, anti-HIV, anti-depressant, and contraceptive activities, etc.[1] Various methods for the preparation of indazoles have been reported. The cyclization of *o*-methylbenzenediazonium salts,[2] *N*-(2-nitrobenzylideneamines),[3] *o*-methyl-*N*-nitrosoanilines,[4] and *o*-acylarylhydrazines[5] or hydrazones of *o*-acylbenzenes[6] is often used, though these classical methods are multistep reactions. Recently, palladium-catalyzed intramolecular amination of *o*-bromobenzylhydrazines giving N-substituted indazoles has also been reported.[7] On the other hand, the [3+2]cycloaddition reaction of diazo compounds such as ethyl diazoacetate[8] and α-diazoketones[9] with benzynes is an attractive strategy for the construction of the indazole nucleus, but these methods are tedious and require the use of explosive *o*-benzenediazonium carboxylates as benzyne precursors.

We have already demonstrated that lithium trimethylsilyldiazomethane (TMSC(Li)N_2), easily prepared from stable and safe trimethylsilyldiazomethane (TMSCHN_2) and *n*-butyllithium or lithium diisopropylamide (LDA), is quite useful as a [C–N–N]azole synthon for the preparation of azoles.[10] For instance, TMSC(Li)N_2 reacts smoothly with α,β-unsaturated nitriles[11] and sulfones,[12] and β-amino-α,β-unsaturated ketones[13] to give the corresponding pyrazoles in high to good yields. Additionally, TMSCHN_2 acts as a [C–N–N]azole synthon in the reaction with 1,4-quinones.[14] As an extension of these works, we now wish to report the [3+2]cycloaddition reaction of TMSC(Li)N_2 with benzynes, generated from halobenzenes, giving 3-trimethylsilylindazoles.

First, we examined the reaction of benzyne generated from nonsubstituted halobenzenes with TMSC(Li)N_2. Treatment of fluorobenzene (1 equiv) and TMSCHN_2 (2 equiv) in the presence of LDA (4 equiv) in Et_2O gave the desired 3-trimethylsilylindazole **1** in 69% yield (entry 1 in Table 1).[15] Replacement of LDA by sterically

Table 1. Synthesis of 3-trimethylsilylindazole (**1**)[a]



1

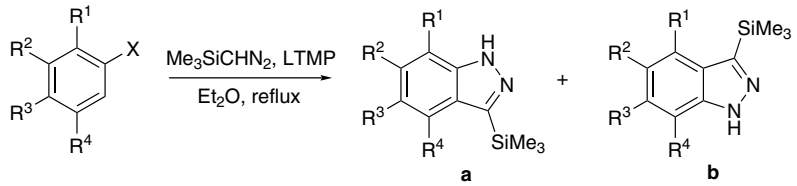
Entry	X	Base	Time (h)	Yield (%)[b]
1	F	LDA	3	69
2	F	LTMP	3	86
3[c]	F	LTMP	3	67
4[d]	F	LTMP	7	54
5	Cl	LTMP	24	78
6	Br	LTMP	24	74
7	I	LTMP	24	41

[a] Me_3SiCHN_2 (2.0 equiv) and LTMP (4.0 equiv) were used.
[b] Isolated yield.
[c] Me_3SiCHN_2 (1.2 equiv) and LTMP (2.4 equiv) were used.
[d] THF in place of Et_2O as a solvent was used.

Keywords: Benzynes; Cycloaddition; Indazoles; Lithium trimethylsilyldiazomethane; Trimethylsilyldiazomethane.
* Corresponding author. Tel./fax: +81-52-836-3439; e-mail: aoyama@phar.nagoya-cu.ac.jp

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.086

Table 2. Synthesis of 3-trimethylsilylindazoles bearing substituents on a benzene ring[a,b]

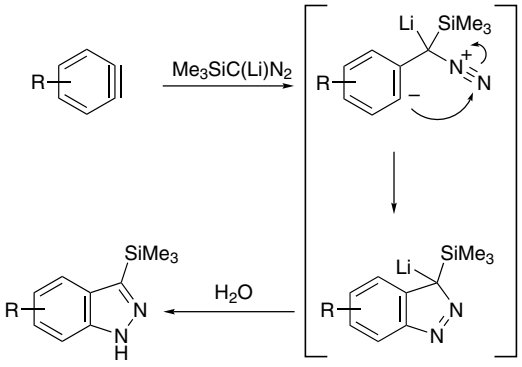


Entry	R^1	R^2	R^3	R^4	X	Time (h)	Yield (%)	Ratio **a**:**b**[c]
1	OMe	H	H	H	F	3	61 (**2a**+**2b**)	73:27[d]
2	OBn	H	H	H	F	8.5	50 (**3a**+**3b**)	75:25[d]
3	NMe_2	H	H	H	Br	48	36 (**4a**+**4b**)	67:33[e]
4	Br	H	H	H	Br	4.5	49 (**5a**+**5b**)	62:38[d]
5	OBu^t	H	H	H	F	1.5	26 (**6a**+**6b**)	83:17[e]
6	Me	H	H	H	F	7.5	65 (**7a**+**7b**)	45:55[d]
7	H	H	OMe	H	F	5	75 (**8a**+**8b**)	50:50[d]
8	H	H	CF_3	H	F	3	74 (**9a**+**9b**)	50:50[d]
9	OMe	H	H	OMe	F	14.5	55 (**10**)	—
10	H	Me	Me	H	F	2	73 (**11**)	—

[a] All products gave satisfactory spectral data and elemental analysis (or HRMS).
[b] Me_3SiCHN_2 (2.0 equiv) and LTMP (4.0 equiv) were used.
[c] The ratio of regioisomers was calculated by ^1H NMR measurement.
[d] The structures of the compounds were determined in comparison with the known compounds after desilylation of the corresponding silylindazoles by treatment with 10% ethanolic KOH.[19]
[e] The structures of the compounds were determined by NOESY measurements.

hindered lithium 2,2,6,6-tetramethylpyperidide (LTMP) caused a significant increase in the yield (86%) (entry 2).[16] Two equivalents of $TMSCHN_2$ was required to conduct the reaction smoothly because a benzyne intermediate is a short-lived reactive species (entries 2 and 3). Et_2O seems to be the solvent of choice though THF can be used (entries 2 and 4). Under the same reaction conditions (entry 2), chloro- and bromo-benzene also reacted with $TMSC(Li)N_2$ to give **1** in good yields (entries 5 and 6) though prolonged reaction time was required. However, the reaction with iodobenzene was extremely slow and the starting material, iodobenzene, did not disappear on TLC after 24 h; consequently, the yield of **1** was moderate (entry 7).

Next, using the optimized reaction conditions (entry 2 in Table 1), the reaction of $TMSC(Li)N_2$ with halobenzenes bearing various substituents was examined (Table 2).[17,18] *o*-Fluoroanisole smoothly reacted with $TMSC(Li)N_2$ to afford the indazoles in 61% yield, but the indazoles obtained were a mixture of 7-methoxy-3-trimethylsilylindazole **2a** and its regioisomer **2b** in good selectivity (**2a**:**2b** = 73:27), probably due to the +I effect of the MeO group (entry 1). Similar regioselectivities were observed in the reaction with *o*-substituted halobenzenes bearing the BnO, Me_2N, and Br groups (entries 2–4).[20] Replacement of the MeO group by the bulky *t*-BuO one increased the regioselectivity (entry 5). The reaction with *o*-fluorotoluene, *p*-fluoroanisole, and *p*-fluoro(trifluoromethyl)benzene also afforded the desired **7a**,**b**, **8a**,**b**, and **9a**,**b** in good yields, though no or little regioselectivity was observed (entries 6–8). The use of 2,5-dimethoxy- and 3,4-dimethyl-fluorobenzene as substrates gave the corresponding indazole **10** and



Scheme 1. Proposed reaction mechanism.

11 as the sole isolable product in good yields, respectively.

The reaction mechanism of this new synthesis of indazoles may be as follows: In analogy with related studies,[21] the first step is a nucleophilic attack of $TMSC(Li)N_2$ to the benzyne. Subsequent cyclization would then produce the indazole intermediate, which is hydrolyzed with water to afford 3-trimethylsilylindazoles as shown in Scheme 1.

In conclusion, the present method using commercially available $TMSCHN_2$ will provide a facile synthesis of indazoles from halobenzenes in one step. Currently, we are investigating the conversion of the trimethylsilyl group of 3-trimethylsilylindazoles into various functional groups.

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research (KAKENHI), a Grant-in-Aid from The Fujisawa Foundation, and a Grant-in-Aid for Research in Nagoya City University.

References and notes

1. For a review, see Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415–2437.
2. (a) Poter, H. D.; Perterson, W. D. In *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, pp 660–661; (b) Bartsch, R. A.; Yang, I.-W. *J. Heterocycl. Chem.* **1984**, *21*, 1063–1064.
3. (a) Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. *J. Chem. Soc.* **1965**, 4831; (b) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375–3380.
4. (a) Kovach, E. G.; Barnes, D. E. *J. Am. Chem. Soc.* **1954**, *76*, 1176–1178; (b) Huisgen, R.; Bast, K. *Org. Synth.* **1962**, *42*, 69–72.
5. Fernandez, P. A.; Bellamy, T.; Kling, M.; Madge, D. J.; Selwood, D. L. *Heterocycles* **2001**, *55*, 1813–1816.
6. (a) Caron, S.; Vazquez, E. *Synthesis* **1999**, 588–592; (b) Lee, F.-Y.; Lien, J.-C.; Huang, L.-J.; Huang, T.-M.; Tsai, S.-C.; Teng, C.-M.; Wu, C.-C.; Cheng, F.-C.; Kuo, S.-C. *J. Med. Chem.* **2001**, *44*, 3746–3749.
7. (a) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519–521; (b) Song, J. J.; Yee, N. K. *Tetrahedron Lett.* **2001**, *42*, 2937–2940.
8. Huisgen, R.; Knorr, R. *Naturwissenschaften* **1961**, *48*, 716.
9. (a) Ried, W.; Schön, M. *Ann. Chem.* **1965**, *689*, 141–144; (b) García-Abbad, E.; García-López, M. T.; García-Muñoz, G.; Stud, M. *J. Heterocycl. Chem.* **1976**, *13*, 1241–1244.
10. For reviews, see (a) Shioiri, T.; Aoyama, T. In *Science of Synthesis*; Fleming, I., Ed.; Georg Thieme: Stuttgart, 2002; Vol. 4, pp 569–577; (b) Shioiri, T.; Aoyama, T. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; JAI: London, 1993; Vol. 1, pp 51–101.
11. Aoyama, T.; Inoue, S.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 433–436.
12. Asaki, T.; Aoyama, T.; Shioiri, T. *Heterocycles* **1988**, *27*, 343–346.
13. Ito, T.; Hatano, K.; Aoyama, T.; Shioiri, T. *Heterocycles* **1993**, *35*, 41–46.
14. Aoyama, T.; Nakano, T.; Nishigaki, S.; Shioiri, T. *Heterocycles* **1990**, *30*, 375–379.
15. Data for 3-trimethylsilylindazole (**1**): Colorless crystals (recrystallization from *n*-hexane). Mp 154–155 °C. IR (neat) ν_{max}: 2986, 1374, 1242, 1048, 847 cm^{-1}. ^1H ($CDCl_3$) δ: 0.46 (9H, s), 7.16 (1H, dd, $J = 8$, 8 Hz), 7.37 (1H, dd, $J = 8$, 8 Hz), 7.54 (1H, d, $J = 8$ Hz), 7.83 (1H, d, $J = 8$ Hz). ^{13}C ($CDCl_3$) δ: −0.7 (×3), 110.1, 120.6, 121.6, 126.2, 128.6, 140.7, 147.5. Mass (EI): m/z 190 (M^+, 41.6), 175 (M^+−Me, 100). Anal. Calcd for $C_{10}H_{14}N_2Si$: C, 63.11; H, 7.41; N, 14.72. Found: C, 62.97; H, 7.43; N, 14.79.
16. Representative procedure: To a solution of lithium tetramethylpiperidide, which was prepared from TMP (0.34 mL, 2.0 mmol) and *n*-BuLi (1.58 M in *n*-hexane, 1.27 mL, 2.0 mmol) in Et_2O (1.5 mL), $TMSCHN_2$ (2.40 M in *n*-hexane, 0.42 mL, 1.0 mmol) was added dropwise under a nitrogen atmosphere at −78 °C and stirred for 15 min. A solution of fluorobenzene (47 μL, 0.5 mmol) in Et_2O (0.5 mL) was added dropwise to a refluxing reaction mixture, and then the whole was heated under reflux for 3 h. After the reaction was quenched by addition of H_2O at 0 °C, a common work-up was carried out. The pure 3-trimethylsilylindazole **1** (81 mg, 86%) as a solid was obtained by flash silica gel column chromatography (*n*-hexane/ethyl acetate = 6:1).
17. Each regioisomer could be separated by flash silica gel column chromatography.
18. Selected data for **2**–**11**. **2a**, ^1H ($CDCl_3$) δ: 0.45 (9H, s), 3.97 (3H, s), 6.72 (1H, d, $J = 8$ Hz), 7.07 (1H, dd, $J = 8$, 8 Hz), 7.39 (1H, d, $J = 8$ Hz); **2b**, ^1H ($CDCl_3$) δ: 0.42 (9H, s), 3.98 (3H, s), 6.47 (1H, d, $J = 8$ Hz), 7.12 (1H, d, $J = 8$ Hz), 7.26–7.31 (1H, m); **3a**, ^1H ($CDCl_3$) δ: 0.46 (9H, s), 5.24 (2H, s), 6.81 (1H, dd, $J = 8$, 8 Hz), 7.06 (1H, dd, $J = 8$, 8 Hz), 7.36–7.48 (6H, m); **3b**, ^1H ($CDCl_3$) δ: 0.43 (9H, s), 5.22 (2H, s), 6.52 (1H, d, $J = 8$ Hz), 7.12 (1H, d, $J = 8$ Hz), 7.37–7.49 (6H, m); **4a**, ^1H ($CDCl_3$) δ: 0.46 (9H, s), 2.95 (6H, s), 6.77 (1H, d, $J = 8$ Hz), 7.07 (1H, dd, $J = 8$, 8 Hz), 7.42 (1H, d, $J = 8$ Hz); **4b**, ^1H ($CDCl_3$) δ: 0.45 (9H, s), 2.78 (6H, s), 6.85 (1H, dd, $J = 2$, 7 Hz), 7.23–7.32 (2H, m); **5a**, ^1H ($CDCl_3$) δ: 0.48 (9H, s), 7.05 (1H, dd, $J = 8$, 8 Hz), 7.52 (1H, d, $J = 8$ Hz), 7.77 (1H, d, $J = 8$ Hz); **5b**, ^1H ($CDCl_3$) δ: 0.57 (9H, s), 7.20 (1H, dd, $J = 8$, 8 Hz), 7.36 (1H, d, $J = 8$ Hz), 7.52 (1H, d, $J = 8$ Hz); **6a**, ^1H ($CDCl_3$) δ: 0.45 (9H, s), 1.47 (9H, s), 6.95 (1H, d, $J = 8$ Hz), 7.05 (1H, dd, $J = 8$, 8 Hz), 7.49 (1H, d, $J = 8$ Hz); **6b**, ^1H ($CDCl_3$) δ: 0.46 (9H, s), 1.68 (9H, s), 6.68 (1H, d, $J = 8$ Hz), 7.05 (1H, d, $J = 8$ Hz), 7.21 (1H, dd, $J = 8$, 8 Hz); **7a**, ^1H ($CDCl_3$) δ: 0.46 (9H, s), 2.57 (3H, s), 7.08–7.16 (2H, m), 7.67 (1H, d, $J = 8$ Hz); **7b**, ^1H ($CDCl_3$) δ: 0.49 (9H, s), 2.73 (3H, s), 6.94 (1H, d, $J = 8$ Hz), 7.23–7.29 (1H, m), 7.39 (1H, d, $J = 8$ Hz); **8a**, ^1H ($CDCl_3$) δ: 0.47 (9H, s), 3.88 (3H, s), 7.07 (1H, dd, $J = 2$, 9 Hz), 7.15 (1H, d, $J = 2$ Hz), 7.47 (1H, d, $J = 9$ Hz); **8b**, ^1H ($CDCl_3$) δ: 0.46 (9H, s), 3.86 (3H, s), 6.82 (1H, dd, $J = 2$, 9 Hz), 6.91 (1H, d, $J = 2$ Hz), 7.67 (1H, d, $J = 9$ Hz); **9a**, ^1H ($CDCl_3$) δ: 0.47 (9H, s), 7.59–7.63 (2H, m), 8.10 (1H, s); **9b**, ^1H ($CDCl_3$) δ: 0.48 (9H, s), 7.37 (1H, d, $J = 8$ Hz), 7.82 (1H, s), 7.92 (1H, d, $J = 8$ Hz); **10**, ^1H ($CDCl_3$) δ: 0.40 (9H, s), 3.92 (3H, s), 3.93 (3H, s), 6.31 (1H, d, $J = 8$ Hz), 6.59 (1H, d, $J = 8$ Hz); **11**, ^1H ($CDCl_3$) δ: 0.45 (9H, s), 2.37 (3H, s), 2.37 (3H, s), 7.29 (1H, s), 7.55 (1H, s).
19. (a) 7-Methoxyindazole: See Ref. 4a; (b) 4-Methoxyindazole and 7-benzyloxyindazole: Schumann, P.; Collot, V.; Hommet, Y.; Gsell, W.; Dauphin, F.; Sopkova, J.; MacKenzie, E. T.; Duval, D.; Boulouard, M.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1153–1156; (c) 7-Bromoindazole: Boulton, B. E.; Coller, B. A. W. *Aust. J. Chem.* **1974**, *27*, 2343–2347; (d) 4-Methylindazole and 5-methoxyindazole: Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1994**, *50*, 3529–3536; (e) 6-(Trifluoromethyl)indazole was synthesized from 2-methyl-5-(trifluoromethyl)aniline commercially available according to Ref. 2b.
20. The reaction of nucleophiles with benzynes generated from halobenzenes bearing substituents such as alkoxy, amino, and halogen groups at the *o*-position, which have +I effect, is well known to give preferentially *m*-substituted benzene derivatives. See: (a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Aoyama, T.; Kusana, O. *J. Org. Chem.* **1971**, *36*, 327–330; (b) Biehl, E. R.; Nieh, E.; Hsu, K. C. *J. Org. Chem.* **1969**, *34*, 3595–3599.
21. Aoyama, T.; Kabeya, M.; Fukushima, A.; Shioiri, T. *Heterocycles* **1985**, *23*, 2363–2366.