A new approach to the one-pot synthesis of 5-substituted 2-methyl-1,3,4-oxadiazoles from *N*-tributylstannyltetrazoles

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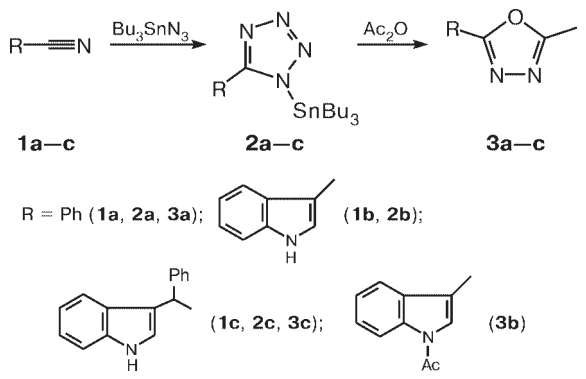
A new approach to the synthesis of 5-substituted 2-methyl-1,3,4-oxadiazoles was developed.

Key words: *N*-tributylstannyltetrazoles, tributylstannyl azide, 5-substituted 2-methyl-1,3,4-oxadiazoles.

Earlier,[1] the antiinflammatory activity of 5-substituted 1,3,4-oxadiazoles and the antiarrhythmia properties of compounds containing a 1,3,4-oxadiazole fragment[2] were studied. 1,3,4-Oxadiazoles are generally synthesized by cyclization of 1,2-diacylated hydrazines. Later,[3] a method for the synthesis of 1,3,4-oxadiazoles from tetrazoles has been proposed. The use of this method is limited since it involves difficultly accessible tetrazoles containing bulky substituents. Recently,[4] the latter have been obtained from tributylstannyl azide. This method allows one to synthesize sterically hindered tetrazoles.

We developed a new approach to the one-pot synthesis of 5-substituted 1,3,4-oxadiazoles from the corresponding tributylstannyl tetrazoles, including sterically hindered ones. The reactions of the corresponding nitriles **1a—c** with Bu_3SnN_3 prepared *in situ* from NaN_3 and Bu_3SnCl gave 5-phenyl-1-(tributylstannyl)tetrazole (**2a**),[5] 3-[1-(tributylstannyl)tetrazol-5-yl]-1*H*-indole (**2b**), and 3-{(phenyl)[1-(tributylstannyl)tetrazol-5-yl]methyl}-1*H*-indole (**2c**) (Scheme 1).

Scheme 1



The reactions of compounds **2a—c** with Ac_2O for 9 h afforded 2-methyl-5-phenyl-1,3,4-oxadiazole (**3a**), 1-acetyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-1*H*-indole (**3b**), and 3-[(5-methyl-1,3,4-oxadiazol-2-yl)(phenyl)methyl]-1*H*-indole (**3c**) in 80, 57, and 53% yields, respectively.

Experimental

^{1}H NMR spectra* were recorded on a Bruker WM-250 spectrometer with Me_4Si as the internal standard. Mass spectra were recorded on a Finnigan MAT SSQ-710 spectrometer (EI, ionizing voltage 70 eV). The course of the reaction was monitored by TLC (Silufol UV-254, EtOAc—CCl_4 (1 : 4) as the eluent). Benzonitrile, 3-cyanoindole, and Bu_3SnCl (Aldrich) and Ac_2O, *o*-xylene, and Pr^iOH (reagent grade) were used.

(Indol-3-yl)phenylacetonitrile was prepared according to the known procedure.[6]

5-Substituted 1-(tributylstannyl)tetrazoles 2a—c (general procedure). A solution of NaN_3 (0.02 mol) and Bu_3SnCl (0.02 mol) in 20 mL of *o*-xylene was refluxed for 5 h and cooled to ~20 °C. Nitrile **1a—c** (0.0065 mol) was added, and the reaction mixture was refluxed for an additional 15 h. The hot solution was filtered to separate inorganic salts, cooled to ~20 °C, and poured into cold light petroleum or hexane. The precipitate that formed was filtered off and washed repeatedly with boiling heptane. Compound **2a** was isolated by flash chromatography in EtOAc—CCl_4 (1 : 4) and then in Pr^iOH.

5-Phenyl-1-(tributylstannyl)tetrazole (2a). Yield 80%, m.p. 66—68 °C (*cf.* Ref. 5: m.p. 66—71 °C).

3-[1-(Tributylstannyl)tetrazol-5-yl]-1*H*-indole (2b). Yield 60%, m.p. 148—150 °C. Found (%): C, 52.89; H, 6.87; N, 14.41. $C_{21}H_{33}N_5Sn$. Calculated (%): C, 53.19; H, 7.01; N, 14.77. ^{1}H NMR (CD_3CN), δ: 0.89 (t, 9 H, 3 Me, J = 7.2 Hz); 1.36—1.68 (m, 18 H, $(CH_2)_9$); 7.19 (m, 1 H, $H(5)_{Ind}$); 7.24 (m,

* The H atoms in the indole fragment are marked with the Ind subscript.

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1 H, $H(6)_{Ind}$); 7.51 (m, 1 H, $H(7)_{Ind}$); 7.85 (d, 1 H, $H(2)_{Ind}$, J = 2.8 Hz); 8.28 (m, 1 H, $H(4)_{Ind}$); 9.60 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 474 $[M]^+$ (10).

3-{(Phenyl)[1-(tributylstannyl)tetrazol-5-yl]methyl}-1*H*-indole (2c). Yield 60%, m.p. 199.5—200.5 °C (Pr^iOH). Found (%): C, 59.59; H, 6.97; N, 12.41. $C_{28}H_{39}N_5Sn$. Calculated (%): C, 59.39; H, 7.07; N, 12.56. ^{1}H NMR (DMSO-d_6), δ: 0.75 (m, 9 H, 3 Me); 1.26 (m, 12 H, 3 $C\underline{H}_2C\underline{H}_2CH_3$); 1.51 (m, 6 H, 3 $C\underline{H}_2(CH_2)_2CH_3$); 5.86 (s, 1 H, CH); 6.85 (m, 1 H, $H(5)_{Ind}$); 7.01 (m, 1 H, $H(6)_{Ind}$); 7.09 (m, 1 H, $H(2)_{Ind}$); 7.12 (m, 1 H, $H(4)_{Ph}$); 7.22 (m, 2 H, $H(3)_{Ph}$, $H(5)_{Ph}$); 7.31 (m, 1 H, $H(7)_{Ind}$); 7.37 (m, 1 H, $H(4)_{Ind}$); 7.43 (m, 2 H, $H(2)_{Ph}$, $H(6)_{Ph}$); 10.82 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 563 $[M]^+$ (15), 206 $[IndCHPh]^+$ (100).

2,5-Disubstituted 1,3,4-oxadiazoles 3a—c (general procedure). Compounds **2a—c** (0.0062 mol) were dissolved in 40 mL of Ac_2O and refluxed for 9 h. The acetic anhydride was removed in a rotary evaporator, and the residue was washed repeatedly with heptane and recrystallized from Pr^iOH.

2-Methyl-5-phenyl-1,3,4-oxadiazole (3a). Yield 80%, m.p. 65—68 °C (Pr^iOH). Found (%): C, 74.42; H, 5.03; N, 14.22. $C_9H_8N_2O$. Calculated (%): C, 74.72; H, 5.23; N, 14.52. ^{1}H NMR (CD_3CN), δ: 2.55 (s, 3 H, Me); 7.60 and 8.01 (both m, 3 H + 2 H, Ph). MS, m/z (I_{rel} (%)): 160 $[M]^+$.

1-Acetyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-1*H*-indole (3b). Yield 57%, m.p. 176—178 °C (Pr^iOH). Found (%): C, 69.74; H, 4.82; N, 10.86. $C_{14}H_{12}N_2O_2$. Calculated (%): C, 69.99; H, 5.03; N, 11.66. ^{1}H NMR (CD_3CN), δ: 2.57 (s, 3 H, Me); 2.68 (s, 3 H, Me); 7.43 (m, 1 H, $H(5)_{Ind}$); 7.49 (m, 1 H, $H(6)_{Ind}$); 8.25 (m, 2 H, $H(4)_{Ind}$ + $H(2)_{Ind}$); 8.45 (m, 1 H, $H(7)_{Ind}$). MS, m/z (I_{rel} (%)): 240 $[M]^+$ (45), 199 $[M - COCH_3]^+$ (100).

3-[(5-Methyl-1,3,4-oxadiazol-2-yl)(phenyl)methyl]-1*H*-indole (3c). Yield 53%, m.p. 185—186 °C (Pr^iOH). Found (%): C, 74.44; H, 5.12; N, 14.26. $C_{18}H_{15}N_3O$. Calculated (%): C, 74.72; H, 5.23; N, 14.52. ^{1}H NMR (CD_3CN), δ: 2.43 (s, 3 H, Me); 5.94 (s, 1 H, CH); 6.99 (m, 1 H, $H(5)_{Ind}$); 7.13 (m, 1 H, $H(6)_{Ind}$); 7.16 (d, 1 H, $H(2)_{Ind}$, J = 2.6 Hz); 7.30—7.40 (m, 5 H, Ph); 7.35 (m, 1 H, $H(4)_{Ind}$); 7.42 (m, 1 H, $H(7)_{Ind}$); 9.35 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 289 $[M]^+$ (100), 206 $[IndCHPh]^+$ (95).

References

1. F. A. Omar, N. M. Mahfouz, and M. A. Rahman, *Eur. J. Med. Chem., Chim. Ther.*, 1996, **31**, 819.
2. G. Adelstein, *J. Med. Chem.*, 1973, **16**, 309.
3. R. Huisgen, *Chem. Ber.*, 1960, **93**, 2106.
4. J. V. Duncia, *J. Org. Chem.*, 1991, **56**, 2395.
5. M. Casey, J. Christopher, and Ch. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1933.
6. K. A. Zaitseva, V. N. Rusinova, Yu. I. Smushkevich, N. N. Suvorov, and M. D. Mashkovskii, *Khim.-Farm. Zh.*, 1973, **10**, 17 [*Pharm. Chem. J.*, 1973, **10** (Engl. Transl.)].

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