The Conversion of Secondary Amides to Tetrazoles with Trifluoromethanesulfonic Anhydride and Sodium Azide

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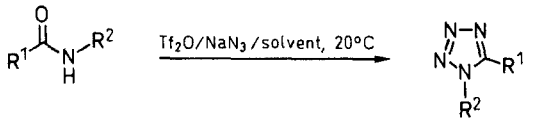
Received 28 December 1992

Due to the interest in tetrazoles as medicinal agents, a new, mild one-step method for the conversion of amides to tetrazoles employing triphenylphosphine, diethyl azodicarboxylate, and trimethylsilyl azide was recently introduced. An alternate and equally simple method employing trifluoromethanesulfonic anhydride and sodium azide was devised. This method was used to synthesize a series of 1,5-substituted tetrazoles from readily available secondary amides. A 1*H*-substituted tetrazole was also synthesized by this method from an amide substituted with a cyanoethyl protecting group.

Tetrazole derivatives are under intense scrutiny as novel hypotensive agents,[1] where the tetrazole is introduced as a carboxylate mimic. A classical synthesis of tetrazoles involves the reaction of an amide with phosphorus(V) chloride to form an imidoyl chloride intermediate.[2-4] This can react with sodium azide or hydrazoic acid to form tetrazoles. Recently, Duncia introduced a new, mild one-step method for the conversion of amides to tetrazoles.[5] He employed triphenylphosphine and diethyl azodicarboxylate (DEAD) to activate the amide toward reaction with trimethylsilyl azide that yielded tetrazoles. We reasoned other mild reagents could activate amides to imidoyl derivatives that could be converted to tetrazoles. Since trifluoromethanesulfonic anhydride (Tf_2O) has been used to form enol triflates from ketones,[6] we reasoned it could also form imidoyl triflates from amides. Others have reacted amides with Tf_2O to yield "dicarbonium salts".[7] We wish to report the results of our studies employing Tf_2O and sodium azide to synthesize tetrazoles.

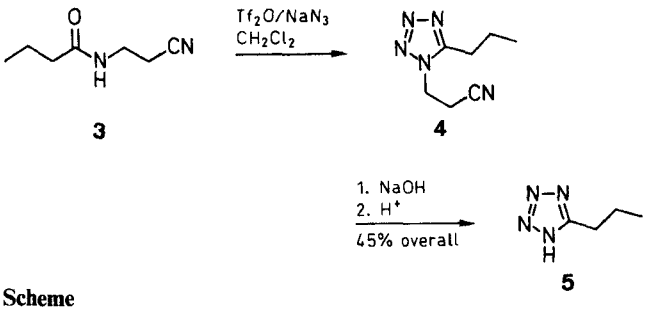
Table. Synthesis of Tetrazoles from Amides



1 **2**

R^1	R^2	Solvent	Yield (%)	1, 2
Me	*c*-C_6H_{11}	CH_2Cl_2	72	**a**
		MeCN	42	**a**
Me	$(CH_2)_2OAc$	CH_2Cl_2	54	**b**
		MeCN	65	**b**
Me	$(CH_2)_2OSiMe_2Bu$-*t*	CH_2Cl_2	0	**c**
		MeCN	4	**c**
t-Bu	Me	CH_2Cl_2	8	**d**
		MeCN	27	**d**
Ph	Me	CH_2Cl_2	34	**e**
		MeCN	45	**e**

Several amides, **1a–e**, were easily prepared or were commercially available. These were dissolved in either dichloromethane or acetonitrile, and then sodium azide and Tf_2O were added to form the 1,5-substituted tetrazoles (Table). During the reaction, sodium azide did not go into solution until the Tf_2O was introduced. The yields of the products were solvent dependent, but no trend was discernible. When amide **1a** was treated with trifluoroacetic anhydride, instead of Tf_2O, and sodium azide in dichloromethane, tetrazole **2a** was not produced. To form a 1-hydrogen-substituted tetrazole (Scheme) compound **4** was synthesized, and the cyanoethyl protecting group was removed affording **5** in 45% overall yield, comparable to the yield of Duncia.[5]



Scheme

The yield of **2c** was improved to 17% when diisopropylethylamine was present in the reaction. The use of a base in the synthesis of tetrazoles via imidoyl chlorides is known to accelerate the reaction.[4,8] Perhaps in this case the base not only accelerates the reaction but buffers the system allowing a slightly greater yield of product.

^1H NMR spectra were recorded at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz. Melting points in open capillaries are uncorrected. All Burdick and Jackson solvents and reagents purchased from Aldrich were used without further purification. All compounds were dried ($MgSO_4$). Solvent was removed on a rotovap under reduced pressure. Unless indicated otherwise, all products were obtained as liquids. Satisfactory microanalyses obtained for **2a, b**: C ± 0.13, H ± 0.26, N ± 0.29, **5**: C − 0.10, H − 0.01; satisfactory HRMS obtained for **2c–e**: $m/z \pm 0.0053$.

1-Cyclohexyl-5-methyl-1*H*-tetrazole (2a): Typical Procedure:
Amide **1a** (141 mg, 1.0 mmol), CH_2Cl_2 (5 mL), and NaN_3 (65 mg, 1.0 mmol) were cooled to 0 °C and Tf_2O (200 µL, 1 mmol) was added.[11] The reaction was warmed to r.t. over 2 h and was continued for an additional 22 h. The reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and was diluted with CH_2Cl_2 (5 mL). The aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic portion was dried and concentrated in vacuo. The material was purified on the Waters' Prep-500 eluting with EtOAc to yield **2a** (121 mg, 72%): mp 122–123 °C (Lit.[3] mp 124–124.5 °C).

^1H NMR ($CDCl_3$): δ = 1.18–1.48 (m, 3H), 1.66–1.77 (m, 1H), 1.84–2.02 (m, 6H), 2.49 (s, 3H, CH_3), 4.00–4.15 (m, 1H, NCH).

^{13}C NMR ($CDCl_3$): δ = 150.2 (s), 57.5 (d), 32.4 (t), 25.1 (t), 24.6 (t), 8.9 (q).

IR (mineral oil mull): ν = 2952, 1524, 1458, 1448, 1384, 819, 769 cm^{-1}.

MS: m/z (%) = 166 (M^+, 4), 138 (2), 109 (3), 95 (32), 85 (55), 82 (59), 67 (56), 55 (100).

1-(2-Acetoxyethyl)-5-methyl-1H-tetrazole **(2b)**:

The crude material was purified on the Waters' Prep-500 eluting with EtOAc to yield **2b** (222 mg, 65%): mp 38–39°C.

^{1}H NMR ($CDCl_3$): δ = 1.98 (s, 3 H, O=CCH_3), 2.53 (s, 3 H, CH_3), 4.43 (d, 2 H, J = 4.5 Hz), 4.49 (d, 2 H, J = 4.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 170.1 (s, O=C), 152.1 (s), 61.8 (t), 45.8 (t), 20.5 (q), 8.8 (q).

IR (mineral oil mull): ν = 2925, 1736, 1528, 1458, 1409, 1274, 1266, 1096, 1039, 655 cm^{-1}.

MS: m/z (%) = 171 (M^+ + H, 1), 128 (9), 110 (4), 98 (19), 87 (10), 69 (30), 55 (66), 43 (100).

1-[2-(tert-Butyldimethylsiloxy)ethyl]-5-methyl-1H-tetrazole **(2c)**:

After addition of amide **1c**, *i*-PrEtN (129 mg, 1.0 mmol) was added and the reaction was conducted as outlined in the typical procedure. The material was purified on the Waters' Prep-500 eluting with EtOAc to yield **2c** (40 mg, 17%).

^{1}H NMR ($CDCl_3$): δ = 0.00 [s, 6 H, $Si(CH_3)_2$], 0.87 (s, 9 H, *t*-Bu), 2.66 (s, 3 H, CH_3), 4.09 (t, 2 H, J = 5 Hz, OCH_2), 4.48 (t, 2 H, J = 5 Hz, CH_2).

MS: m/z (%) = 243 (M^+, 100), 217 (23), 185 (28), 73 (78).

5-tert-Butyl-1-methyl-1H-tetrazole **(2d)**:

The pink oil was purified on the Waters' Prep-500 eluting with EtOAc to yield **2d** (149 mg, 27%): mp 54–55°C (Lit.[9] mp 62–64°C).

^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 9 H, *t*-Bu), 4.09 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 160.8 (s), 35.7 (q), 31.0 (s), 28.3 (q).

IR (mineral oil mull): ν = 2982, 1622, 1598, 1507, 1436, 1209, 1160, 1029, 705 cm^{-1}.

MS: m/z (%) = 272 (22), 140 (M^+, 50), 113 (9), 84 (22), 69 (31), 57 (100). Recrystallization of **2d** from Et_2O did not remove peak at 272 in MS.

1-Methyl-5-phenyl-1H-tetrazole **(2e)**:

The material was purified on the Waters' Prep-500 eluting with EtOAc to yield **2e** (72 mg, 45%): mp 95–97°C.

^{1}H NMR ($CDCl_3$): δ = 4.19 (s, 3 H, CH_3), 7.55–7.62 (m, 3 H_{arom}), 7.71–7.80 (m, 2 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 154.3 (s), 131.2 (d), 129.1 (d), 128.5 (d), 123.6 (s), 34.9 (q).

IR (mineral oil mull): ν = 2925, 1607, 1540, 1474, 1468, 1328, 1292, 1213, 1116, 782, 734, 703 cm^{-1}.

MS: m/z (%) = 160 (M^+, 100), 131 (29), 118 (76), 90 (51), 77 (58).

Recrystallized from Et_2O; mp 100–102°C (Lit.[9] mp 102–104°C).

5-Propyl-1*H*-tetrazole (5):

Amide **3** (280 mg, 2.0 mmol), CH_2Cl_2 (10 mL), and NaN_3 (130 mg, 2.0 mmol) were cooled to 0°C and Tf_2O (400 µL, 2 mmol) was added. The reaction was warmed to r.t. over 2 h and was continued for an additional 22 h. The reaction was quenched with sat. aq $NaHCO_3$ (10 mL) and was diluted with CH_2Cl_2 (20 mL). The aqueous portion was extracted with CH_2Cl_2 (3 × 20 mL). The organic portion was dried and concentrated in vacuo to yield 300 mg of **4**.

^{1}H NMR ($CDCl_3$): δ = 1.07 (t, 3 H, J = 7.4 Hz, CH_3), 1.84–2.00 (m, 2 H, CH_2), 2.89 (t, 2 H, J = 7.4 Hz, $=CCH_2$), 3.11 (t, 2 H, J = 6.6 Hz, CH_2CN), 4.57 (t, 2 H, J = 6.6 Hz, NCH_2).

The nitrile **4** (300 mg), MeOH (10 mL), and 10% NaOH (2 mL) were combined and stirred at r.t. for 3.5 h. The reaction was concentrated in vacuo and dissolved in H_2O (2 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The aqueous portion was acidified to a pH of 2 with 10% HCl. This was extracted with CH_2Cl_2 (3 × 20 mL), dried and concentrated affording **5** (101 mg, 45% overall) as a waxy solid: mp 56–58°C (Lit.[10] mp 63–64°C).

^{1}H NMR ($CDCl_3$): δ = 0.95 (t, 3 H, J = 7.3 Hz, CH_3), 1.76–1.93 (m, 2 H, CH_2), 3.06 (t, 2 H, J = 7.5 Hz, $=CCH_2$), 14.05 (br s, 1 H, NH).

IR (mineral oil mull): ν = 2923, 1811, 1579, 1444, 1420, 1076, 1049, 990, 915 cm^{-1}.

MS: m/z (%) = 113 (M^+ + H, 3), 97 (8), 84 (86), 69 (12), 55 (100).

We are grateful to The Upjohn Company's Physical and Analytical Chemistry Department for elemental anaylses, mass spectra, and IR spectroscopy.

(1) Wong, P.C.; Price, Jr. W.A.; Chiu, A.T.; Duncia, J.V.; Carini, D.J.; Wexler, R.R.; Johnson, A.L.; Timmermans, P.B. *Hypertension* **1990**, *15*, 459.
(2) von Braun, J.; Rudolf, W. *Chem. Ber.* **1941**, *74*, 264.
(3) Harvill, E.K.; Herbst, R.M.; Schreiner, E.C.; Roberts, C.W. *J. Org. Chem.* **1950**, *15*, 662.
(4) Butler, R.N. In *Advances in Heterocyclic Chemistry*; Katritzky, A.R.; Boulton, A.J., Eds.; Academic: New York, 1977; Vol. 21, p 378.
(5) Duncia, J.V.; Pierce, M.E.; Stantella, III, J.B. *J. Org. Chem.* **1991**, *56*, 2395.
(6) Dueber, T.E.; Stang, P.J.; Pfeifer, W.D.; Summerville, R.H.; Imhoff, M.A.; Schleyer, P.R.; Hummel, K.; Bocher, S.; Harding, C.E.; Hanack, M. *Angew. Chem.* **1970**, *82*, 517; *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 521.
(7) Gramstad, T.; Husebye, S.; Saebo, J. *Tetrahedron Lett.* **1983**, *24*, 3919.
(8) Butler, R.N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A.R., Ed.; Pergamon: Oxford, 1984; Vol. 5, p 825.
(9) Spear, R.J. *Aust. J. Chem.* **1984**, *37*, 2453.
(10) Finnegan, W.G.; Henry, R.A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *50*, 3908.
(11) Explosions have been reported with reactions involving sodium azide and dichloromethane. See Peet, N.P.; Weintraub, P.M. *Chem. Eng. News.* **1993**, *71(16)*, 4. When possible acetonitrile should be substituted for dichloromethane.