Synthesis of 1,5-Disubstituted 1*H*-Tetrazole Derivatives *via* a Three-Component Reaction of Carbodiimides, Isocyanides, and Trimethylsilyl Azide

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The three-component reaction of isocyanides **1**, carbodiimides **2**, and trimethylsilyl azide (**3**) occurs at room temperature, and the produced 1,5-disubstituted 1*H*-tetrazole derivatives **4** are formed in 81–98% yields (*Scheme 1*, *Table*). The reaction proceeds smoothly and cleanly under mild conditions, and no side reactions are observed.

Introduction. – Tetrazoles are important heterocycles in medicinal chemistry. They have been known as an HIV-1 protease inhibitor and as antihypertensive, anti-allergic, antibiotic, and anticancer agents [1]. Multicomponent reactions (MCRs) are processes in which three or more reactants are combined in a single chemical transformation to produce products that incorporate substantial portions of all the components [2]. Multicomponent reactions are very useful and important for the construction of diverse organic compounds. An important class of MCRs are the isocyanide-based multi-component reactions (abbreviated to IMCRs by *Ugi* and *Dömling*). IMCRs are especially interesting because they are more diverse and versatile than nonisocyanide-based multicomponent reactions [2–6]. IMCRs were introduced in 1921 by *Passerini* [7]. They have been shown to enable the synthesis of various heterocycles [8]. In connection with our interest in the synthesis of heterocycles [9][10] and isocyanide chemistry [11], we report a three-component reaction of isocyanides **1**, carbodiimides **2**, and trimethylsilyl azide (**3**) leading to 1,5-disubstituted 1*H*-tetrazole derivatives **4**.

Results and Discussion. – The isocyanides **1**, carbodiimides **2**, and trimethylsilyl azide (**3**) reacted in a 1:1:1 ratio in MeOH at room temperature *via* a three-component reaction to give 1,5-disubstituted 1*H*-tetrazole derivatives **4a**–**4f** (*Scheme 1*, *Table*). The reaction proceeded smoothly and cleanly, and the products obtained did not require any purification. The structures of the products were deduced from their IR, ^{1}H- and ^{13}C-NMR spectra, and mass spectra and elemental analyses. For example, the ^{1}H-NMR spectrum of **4a** exhibited distinct signals arising from Me groups of two ^{i}Pr residues (δ(H) 1.16 and 1.37), and a ^{t}Bu group (δ(H) 1.61), from CH of the ^{i}Pr groups (δ(H) 3.91 and 4.44), and from a NH moiety (δ(H) 5.14). The NH exchanged after D_2O addition, and its signal disappeared. The ^{13}C-NMR spectrum of **4a** showed 8 distinct resonances arising from the 4 Me of ^{i}Pr (δ(C) 21.58 and 22.64),

Me$_3$C (δ(C) 29.60), 2 CH of ^{i}Pr (δ(C) 46.42 and 48.27), Me$_3$*C* (δ(C) 59.72), and 2 C=N (δ(C) 140.10 and 154.11). The IR spectrum showed a NH absorption at 3277 cm^{-1}. The mass spectrum of **4a** displayed a molecular-ion peak at *m*/*z* 252.

Scheme 1. *Three-Component Reaction of Isocyanides, Carbodiimides, and Trimethylsilyl Azide.* For R^1 and R^2, see the *Table*.

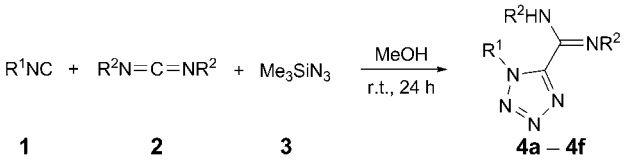
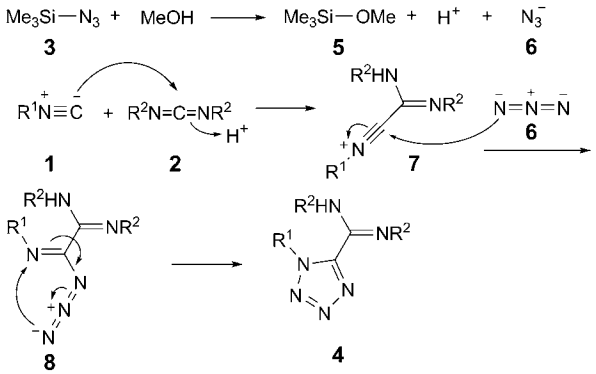


Table. *Synthesis of 1,5-Disubstituted 1*H*-Tetrazole Derivatives* **4a**–**4f**

R^1	R^2	Product	Yield [%]
^{t}Bu	^{i}Pr	**4a**	93
1,1,3,3-Tetramethylbutyl	^{i}Pr	**4b**	98
Cyclohexyl	^{i}Pr	**4c**	82
^{t}Bu	cyclohexyl	**4d**	93
1,1,3,3-Tetramethylbutyl	cyclohexyl	**4e**	97
Cyclohexyl	cyclohexyl	**4f**	81

A mechanistic rationalization for this reaction is depicted in *Scheme 2*. The first step is the *in situ* generation of hydrazoic acid (HN_3) from the reaction between trimethylsilyl azide (**3**) and MeOH. On the basis of isocyanide chemistry, the nucleophilic addition of isocyanide **1** to carbodiimide **2** and protonation of the resulting adduct leads to the nitrilium intermediate **7**. This intermediate may be attacked by the azide anion **6** to form the adduct **8**, and finally the ring closing of the latter gives 1*H*-tetrazole derivative **4**.

Scheme 2. *Proposed Mechanism for the Formation of 1,5-Disubstituted 1*H*-Tetrazoles* **4a**–**4f**



Conclusions. – We presented a mild, simple, and efficient route for the synthesis of 1,5-disubstituted 1*H*-tetrazole derivatives **4** *via* a three-component reaction of

isocyanides **1**, carbodiimides **2**, and trimethylsilyl azide (**3**). The ease of workup, high yields, and fairly mild reaction conditions render this reaction a useful addition to modern synthetic methodologies.

Experimental Part

General. Starting materials and solvents were obtained from *Merck* (Germany) and *Fluka* (Switzerland) and were used without further purification. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *Jasco-FT-IR 6300* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-250-Avance* spectrometer (250.0 and 62.5 MHz, resp.), in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS: *HP 5937* (*Agilent Technologies*) mass selective detector; ionization potential 70 eV; in *m*/*z*. Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer.

General Procedure. To a magnetically stirred soln. of isocyanide **1** (0.2 mmol) and carbodiimide **2** (0.2 mmol) in MeOH (3 ml) was added trimethylsilyl azide (**3**; 0.2 mmol). The mixture was stirred at r.t. for 24 h. The solvent was evaporated to give the pure product.

*1-(*tert-*Butyl)*-N^5,N′^{5}-*diisopropyl-1*H-*tetrazole-5-carboximidamide* (**4a**): Yield 93%. White solid. M.p. 105.4–107.9°. IR (KBr): 3277 (NH), 2980, 1594, 1465, 1099. ^{1}H-NMR: 1.16 (*d*, *J* = 6.5, 1 *Me*$_2$CH); 1.37 (*d*, *J* = 6.5, 1 *Me*$_2$CH); 1.61 (*s*, Me_3C); 3.91 (*m*, *J* = 6.5, 1 Me_2C*H*); 4.44 (*sept.*, *J* = 6.5, 1 Me_2C*H*); 5.14 (*d*, *J* = 6, NH). ^{13}C-NMR: 21.58; 22.64 (1 *Me*$_2$CH); 29.60 (*Me*$_3$C); 46.42, 48.27 (1 Me_2C*H*); 59.72 (Me_3*C*), 140.10; 154.11 (2 C=N). EI-MS: 252 (*M*$^+$, 2), 212 (27), 171 (12), 170 (100), 128 (10), 58 (8), 43 (26). Anal. calc. for $C_{12}H_{24}N_6$ (252.36): C 57.11, H 9.59, N 33.30; found: C 57.04, H 9.57, N 33.35.

N^5,N′^{5}-*Diisopropyl-1-(1,1,3,3-tetramethylbutyl)-1*H-*tetrazole-5-carboximidamide* (**4b**): Yield 98%. White solid. M.p. 111.1–112.5°. IR (KBr): 3268 (NH), 2979, 1598, 1467, 1147. ^{1}H-NMR: 0.67 (*s*, Me_3C); 1.20 (*d*, *J* = 6.25, 1 *Me*$_2$CH); 1.41 (*d*, *J* = 6.5, 1 *Me*$_2$CH); 1.70 (*s*, Me_2C); 1.98 (*s*, CH_2); 3.93 (*m*, *J* = 7, 1 Me_2C*H*); 4.44 (*sept.*, *J* = 6.5, 1 Me_2C*H*); 5.11 (*d*, *J* = 7.25, NH). ^{13}C-NMR: 21.62; 22.69 (2 *Me*$_2$CH); 29.80 (*Me*$_2$C); 30.48 (*Me*$_3$C); 31.44 (Me_3*C*); 46.46, 48.31 (2 Me_2C*H*); 54.12 (CH_2); 62.93 (Me_2*C*); 140.78; 154.13 (2 C=N). EI-MS: 308 (*M*$^+$, 1), 290 (5), 183 (58), 107 (52), 91 (100), 65 (23), 57 (13), 43 (14). Anal. calc. for $C_{16}H_{32}N_6$ (308.47): C 62.30, H 10.46, N 27.24; found: C 62.36, H 10.42, N 27.19.

1-Cyclohexyl-N^5,N′^{5}-*diisopropyl-1*H-*tetrazole-5-carboximidamide* (**4c**): Yield 82%. White solid. M.p. 111.9–113.4°. IR (KBr): 3289, 2938, 1593, 1455, 1168. ^{1}H-NMR: 1.20 (*d*, *J* = 6.25, 1 *Me*$_2$CH); 1.42 (*d*, *J* = 6.5, 1 *Me*$_2$CH); 1.22–2.19 (*m*, 5 CH_2 of Chx); 3.94 (*m*, 1 Me_2C*H*); 4.33–4.54 (*m*, 1 Me_2C*H*, CH of Chx); 4.99 (*d*, *J* = 6.5, NH). ^{13}C-NMR: 21.60, 22.71 (2 *Me*$_2$CH); 24.73, 24.75, 32.96 (5 CH_2 of Chx); 46.48; 48.35 (2 Me_2C*H*); 58.80 (CH of Chx), 140.96, 154.07 (2 C=N). Anal. calc. for $C_{14}H_{26}N_6$ (278.40): C 60.40, H 9.41, N 30.19; found: C 60.34, H 9.39, N 30.22.

*1-(*tert-*Butyl)*-N^5,N′^{5}-*dicyclohexyl-1*H-*tetrazole-5-carboximidamide* (**4d**). Yield 93%. White solid. M.p. 122.3–124.4°. IR (KBr): 3313 (NH), 2926, 1594, 1444, 1102. ^{1}H-NMR: 1.11–2.07 (*m*, 10 CH_2 of Chx); 1.67 (*s*, Me_3C); 3.54–3.73 (*m*, CH of Chx); 3.84–4.01 (*m*, CH of Chx); 4.71 (*d*, *J* = 5.5, NH). ^{13}C-NMR: 24.87, 24.97, 25.05, 25.50, 31.83, 33.25 (10 CH_2 of Chx); 29.70 (*Me*$_3$C); 53.46, 55.34 (2 CH of Chx); 59.69 (Me_3*C*); 139.97, 153.96 (2 C=N). EI-MS: 332 (*M*$^+$, 2), 290, 249, 221, 168, 83, 55. Anal. calc. for $C_{18}H_{32}N_6$ (332.49): C 65.02, H 9.70, N 25.28; found: C 64.97, H 9.66, N 25.34.

N^5,N′^{5}-*Dicyclohexyl-1-(1,1,3,3-tetramethylbutyl)-1*H-*tetrazole-5-carboximidamide* (**4e**): Yield 97%. White solid. M.p. 65.8–66.2°. IR (KBr): 3313, 2926, 1594, 1445, 1100. ^{1}H-NMR: 0.69 (*s*, Me_3C); 1.07–2.04 (*m*, 10 CH_2 of Chx); 1.71 (*s*, Me_2C); 1.99 (*s*, CH_2); 3.51–3.68 (*m*, CH of Chx); 3.93–4.08 (*m*, CH of Chx); 5.15 (*d*, *J* = 7.5, NH). ^{13}C-NMR: 24.88, 24.98, 25.02, 25.47, 31.86, 33.14 (10 CH_2 of Chx); 29.82 (*Me*$_2$C); 30.50 (*Me*$_3$C); 31.46 (Me_3*C*); 53.52, 55.17 (2 CH of Chx); 54.11 (CH_2); 62.90 (Me_2*C*); 140.74, 154.11 (2 C=N). Anal. calc. for $C_{22}H_{40}N_6$ (388.59): C 68.00, H 10.38, N 21.63, found: C 68.07, H 10.34, N 21.60.

N^5,N′^{5},*1-Tricyclohexyl-1*H-*tetrazole-5-carboximidamide* (**4f**): Yield 81%. White solid. M.p. 72.4–74.1°. IR (KBr): 3313 (NH), 2926, 1594, 1444, 1101. ^{1}H-NMR: 1.18–2.16 (*m*, 15 CH_2 of Chx); 3.48–5.18 (4*m*, 3 CH of Chx, NH). ^{13}C-NMR: 24.73, 24.84, 24.97, 25.06, 25.44, 31.82, 32.95, 32.99, 33.11 (15 CH_2 of Chx); 53.62, 55.47, 58.76 (3 CH of Chx); 140.92, 153.98 (2 C=N). Anal. calc. for $C_{20}H_{34}N_6$ (358.52): C 67.00, H 9.56, N 23.44; found: C 67.06, H 9.58, N 23.40.

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