

Copper-Catalyzed Synthesis of Alkynyl Hydrazones from Alkynes and Hydrazonyl Chlorides

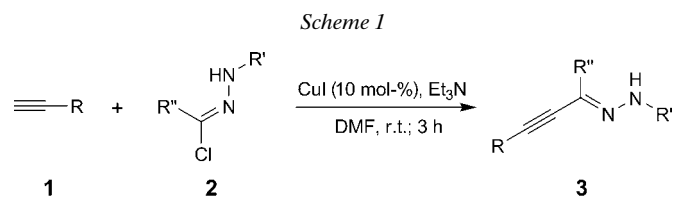
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A novel ligand-free synthesis of alkynyl hydrazones *via* coupling reaction of hydrazonyl chlorides and terminal alkynes, catalyzed by CuI led to excellent yields.

Introduction. – Alkynyl hydrazones are versatile intermediates, which are used in heterocyclic synthesis [1][2]. Alkynyl hydrazones are successfully converted to the corresponding 3-aminoacrylonitriles in the presence of copper catalysts [3]. Despite the synthetic importance of alkynyl hydrazones, relatively few methods are available for their synthesis. Alkynyl hydrazones have been prepared from propargyl aldehydes and hydrazines [4].

Herein, we report a simple and efficient procedure for the synthesis of alkynyl hydrazones *via* the Cu-catalyzed coupling reaction of hydrazonyl chlorides [5] and terminal alkynes (*Scheme 1*).



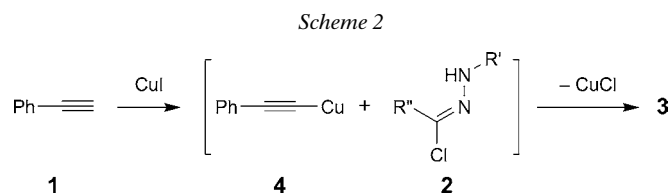
1 – 3	R	R'	R''	Yield [%] of 3
a	Ph	Ph	Ph	91
b	Ph	Ph	4-Me-C ₆ H ₄	87
c	Ph	Ph	4-Cl-C ₆ H ₄	85
d	Ph	4-O ₂ N-C ₆ H ₄	Ph	90
e	Ph	4-O ₂ N-C ₆ H ₄	4-Me-C ₆ H ₄	86
f	Ph	4-O ₂ N-C ₆ H ₄	4-Cl-C ₆ H ₄	83
g	Pr	Ph	Ph	79
h	Pr	Ph	4-Cl-C ₆ H ₄	76
i	Bu	Ph	4-Cl-C ₆ H ₄	72

Results and Discussion. – Initially, phenylacetylene (=ethynylbenzene; **1a**) and (*E*)-1-[chloro(phenyl)methylidene]-2-phenylhydrazine (= *N*-phenylbenzenecarbohydrazonyl chloride; **2a**) were selected as the model substrates. Several catalysts such

as CuI, CuBr, CuCl, and Cu powder were tested with CuI giving the best results. Among several solvents screened, (DMF) was the best. When the reaction was performed in DMF in the presence of 1 equiv. of Et₃N at room temperature for 3 h, the desired product **3a** was obtained in 91% yield (*Scheme 1*). Thus, the optimized reaction conditions used were 10 mol-% of CuI, 1 mmol of alkyne **1**, 1 mmol of Et₃N, and 1 mmol of hydrazonyl chloride **2** in DMF at room temperature.

Structures of compounds **3a–3i** were assigned by IR, ¹H- and ¹³C-NMR, and MS data. The ¹H-NMR spectrum of **3a** exhibited one *singlet* for NH (δ (H) 8.74), along with characteristic *multiplets* for the Ph H-atoms. The ¹³C-NMR spectrum of **3a** exhibited 15 signals in agreement with the proposed structure. The mass spectrum of **3a** displayed the molecular ion peak at *m/z* 296. The NMR spectra of products **3b–3i** were similar to those of **3a**, except for the substituents.

A mechanism for the formation of products **3** is proposed in *Scheme 2*. The yellow copper acetylide **4**, formed from **1** and CuI, undergoes nucleophilic addition reaction with **2** to afford alkynyl hydrazone **3**.



In conclusion, we have demonstrated that CuI-catalyzed coupling reaction, of hydrazonyl chlorides with terminal alkynes afford a novel and efficient ligand-free synthesis of alkynyl hydrazones. The potential diversity of this type of reaction and available starting materials and catalysts are the main advantages of this methodology.

Experimental Part

General. All chemicals were obtained commercially and used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-460* spectrometer; in cm⁻¹. ¹H- and ¹³C-NMR spectra: *Bruker DRX-500 Avance* instrument at 500.1 and 125.7 MHz, resp.; δ in ppm, *J* in Hz. MS: *Finnigan-MAT-8430EI-MS* mass spectrometer; at 70 eV; in *m/z* (rel. %). Elemental analyses: *Vario EL III CHNOS* elemental analyzer.

General Procedure for the Synthesis of Compounds 3. A mixture of alkyne **1** (1 mmol), CuI (0.1 mmol), and Et₃N (1 mmol) in DMF (3 ml) was slowly added to hydrazonyl chloride **2** (1 mmol), and stirred at r.t. under N₂. After completion of the reaction (*ca.* 3 h; TLC (AcOEt/hexane 1:7) monitoring), the mixture was diluted with CH₂Cl₂ (2 ml) and aq. NH₄Cl soln. (3 ml), stirred for 30 min, and the layers were separated. The aq. layer was extracted with CH₂Cl₂ (3 × 3 ml) and the combined org. fractions were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash CC (SiO₂ (230–400 mesh; *Merck*), hexane/AcOEt 7:1) to give the product.

1-(1,3-Diphenylprop-2-yn-1-ylidene)-2-phenylhydrazine (3a). Yield: 0.27 g (91%). Yellow solid. M.p. 116–118°. IR (KBr): 3332, 2100, 1593, 1506, 1327, 1250, 1157. ¹H-NMR: 6.98 (*t*, *J* = 7.3, 1 arom. H); 7.24 (*d*, *J* = 8.2, 2 arom. H); 7.32 (*t*, *J* = 7.3, 2 arom. H); 7.38 (*d*, *J* = 7.3, 2 arom. H); 7.44–7.47 (*m*, 4 arom. H); 7.65 (*d*, *J* = 7.3, 2 arom. H); 7.93 (*d*, *J* = 8.2, 2 arom. H); 8.74 (*s*, NH). ¹³C-NMR: 78.5 (C); 104.1 (C); 113.6 (2 CH); 121.4 (CH); 124.6 (C); 126.7 (2 CH); 126.8 (CH); 128.6 (2 CH); 128.8 (2 CH); 129.4 (2 CH); 129.8 (CH); 131.9 (2 CH); 133.8 (C); 134.5 (C); 143.4 (C). MS: 296 (15, *M*⁺), 219 (25), 204 (42),

195 (32), 101 (100), 92 (70), 77 (54). Anal. calc. for $C_{21}H_{16}N_2$ (296.13): C 85.11, H 5.44, N 9.45; found: C 85.45, H 5.41, N 9.51.

1-[1-(4-Methylphenyl)-3-phenylprop-2-yn-1-ylidene]-2-phenylhydrazine (3b). Yield: 0.27 g (87%). Yellow solid. M.p. 119–121°. IR (KBr): 3738, 2112, 1595, 1507, 1255, 1110. 1H -NMR: 2.44 (s, Me); 6.98 (t, $J = 7.3$, 1 arom. H); 7.24–7.29 (m, 4 arom. H); 7.35 (t, $J = 7.3$, 2 arom. H); 7.45–7.50 (m, 3 arom. H); 7.68 (t, $J = 7.3$, 2 arom. H); 7.94 (d, $J = 8.1$, 2 arom. H); 8.73 (s, NH). ^{13}C -NMR: 21.3 (Me); 79.1 (C); 103.5 (C); 113.5 (2 CH); 121.0 (CH); 121.7 (C); 125.5 (2 CH); 126.0 (C); 128.7 (2 CH); 128.9 (2 CH); 129.3 (2 CH); 129.6 (CH); 131.9 (2 CH); 133.3 (C); 138.1 (C); 143.8 (C). MS: 310 (10, M^+), 233 (25), 218 (21), 101 (100), 92 (45), 91 (50), 77 (55). Anal. calc. for $C_{22}H_{18}N_2$ (310.15): C 85.13, H 5.85, N 9.03; found: C 85.51, H 5.90, N 9.09.

1-[1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ylidene]-2-phenylhydrazine (3c). Yield: 0.26 g (85%). Yellow solid. M.p. 120–123°. IR (KBr): 3433, 2114, 1577, 1519, 1325, 1254, 1117. 1H -NMR: 6.98 (t, $J = 7.3$, 1 arom. H); 7.25 (d, $J = 7.3$, 2 arom. H); 7.34–7.42 (m, 5 arom. H); 7.48 (d, $J = 7.6$, 2 arom. H); 7.65 (d, $J = 8.1$, 2 arom. H); 7.93 (d, $J = 8.1$, 2 arom. H); 8.75 (s, NH). ^{13}C -NMR: 78.5 (C); 104.1 (C); 113.6 (2 CH); 121.3 (CH); 124.5 (C); 126.7 (2 CH); 127.5 (2 CH); 127.9 (C); 128.7 (2 CH); 129.4 (2 CH); 129.7 (2 CH); 131.9 (CH); 133.8 (C); 134.5 (C); 143.4 (C). MS: 330 (16, M^+), 253 (42), 238 (50), 111 (35), 101 (100), 92 (30), 77 (65). Anal. calc. for $C_{21}H_{15}N_2Cl$ (330.81): C 76.24, H 4.57, N 8.47; found: C 76.71, H 4.62, N 8.85.

1-(1,3-Diphenylprop-2-yn-1-ylidene)-2-(4-nitrophenyl)hydrazine (3d). Yield: 0.31 g (90%). Yellow solid. M.p. 154–156°. IR (KBr): 3535, 2111, 1591, 1499, 1358, 1252. 1H -NMR: 7.00 (t, $J = 7.3$, 1 arom. H); 7.26 (d, $J = 7.3$, 2 arom. H); 7.29 (t, $J = 7.6$, 2 arom. H); 7.41–7.49 (m, 5 arom. H); 7.70 (d, $J = 8.1$, 2 arom. H); 8.12 (d, $J = 8.1$, 2 arom. H); 8.79 (s, NH). ^{13}C -NMR: 79.0 (C); 103.8 (C); 113.4 (2 CH); 120.3 (CH); 121.2 (C); 125.7 (2 CH); 127.7 (C); 128.3 (CH); 128.5 (2 CH); 128.8 (2 CH); 129.8 (2 CH); 131.9 (2 CH); 132.5 (C); 135.9 (C); 143.8 (C). MS: 341 (17, M^+), 264 (26), 240 (22), 137 (31), 101 (100), 91 (57), 77 (40). Anal. calc. for $C_{21}H_{15}N_3O_2$ (341.12): C 73.89, H 4.43, N 12.31; found: C 73.56, H 4.47, N 12.38.

1-[1-(4-Methylphenyl)-3-phenylprop-2-yn-1-ylidene]-2-(4-nitrophenyl)hydrazine; (3e). Yield: 0.31 g (86%). Yellow solid. M.p. 131–133°. IR (KBr): 3256, 2115, 1592, 1500, 1401, 1257. 1H -NMR: 2.43 (s, Me); 6.97 (t, $J = 7.3$, 1 arom. H); 7.25–7.30 (m, 4 arom. H); 7.36 (t, $J = 7.3$, 2 arom. H); 7.48 (d, $J = 7.3$, 2 arom. H); 7.68 (d, $J = 8.1$, 2 arom. H); 7.92 (d, $J = 8.1$, 2 arom. H); 8.72 (s, NH). ^{13}C -NMR: 21.3 (Me); 79.1 (C); 103.5 (C); 113.5 (2 CH); 120.9 (C); 121.7 (C); 125.5 (2 CH); 126.0 (C); 128.7 (2 CH); 128.8 (2 CH); 129.1 (2 CH); 129.7 (CH); 131.9 (2 CH); 133.2 (C); 138.1 (C); 143.8 (C). MS: 355 (17, M^+), 264 (38), 233 (26), 137 (62), 101 (100), 91 (70), 77 (67). Anal. calc. for $C_{22}H_{17}N_3O_2$ (355.39): C 74.35, H 4.82, N 9.00; found: C 74.69, H 4.85, N 9.11.

1-[1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ylidene]-2-(4-nitrophenyl)hydrazine (3f). Yield: 0.31 g (83%). Yellow solid. M.p. 161–163°. IR (KBr): 3431, 2115, 1590, 1507, 1404, 1258. 1H -NMR: 6.96 (t, $J = 7.3$, 1 arom. H); 7.20–7.27 (m, 4 arom. H); 7.35 (t, $J = 7.6$, 2 arom. H); 7.46 (d, $J = 7.6$, 2 arom. H); 7.67 (d, $J = 8.1$, 2 arom. H); 7.93 (d, $J = 8.1$, 2 arom. H); 8.71 (s, NH). ^{13}C -NMR: 79.1 (C); 103.5 (C); 113.5 (2 CH); 120.9 (CH); 121.7 (C); 125.7 (2 CH); 126.0 (C); 128.3 (2 CH); 128.6 (2 CH); 129.1 (2 CH); 129.6 (C); 131.9 (2 CH); 133.2 (C); 138.2 (C); 143.8 (C). MS: 375 (10, M^+), 294 (24), 264 (62), 111 (100), 101 (54), 77 (57). Anal. calc. for $C_{21}H_{14}ClN_3O_2$ (375.08): C 67.12, H 3.75, N 11.18; found: C 67.39, H 3.79, N 11.14.

1-Phenyl-2-(1-phenylhex-2-yn-1-ylidene)hydrazine (3g). Yield: 0.21 g (79%). Yellow solid. M.p. 101–103°. IR (KBr): 3250, 2142, 1576, 1516, 1435, 1367, 1150. 1H -NMR: 1.14 (t, $J = 6.2$, Me); 1.74–1.81 (m, CH_2); 2.62 (t, $J = 6.8$, CH_2); 6.93 (t, $J = 7.2$, 1 arom. H); 7.21 (d, $J = 7.2$, 2 arom. H); 7.30–7.39 (m, 5 arom. H); 7.85 (t, $J = 7.2$, 2 arom. H); 8.62 (s, NH). ^{13}C -NMR: 13.6 (Me); 21.7 (CH_2); 22.1 (CH_2); 70.9 (C); 106.1 (C); 113.4 (2 CH); 120.9 (CH); 125.3 (CH); 126.6 (2 CH); 128.7 (2 CH); 129.3 (2 CH); 133.6 (C); 134.7 (C); 143.6 (C). MS: 262 (22, M^+), 219 (16), 195 (32), 92 (100), 77 (42), 67 (50). Anal. calc. for $C_{18}H_{18}N_2$ (262.35): C 82.41, H 6.92, N 10.68; found: C, 82.22; H, 6.87; N, 10.92.

1-[1-(4-Chlorophenyl)hex-2-yn-1-ylidene]-2-phenylhydrazine (3h). Yield: 0.22 g (76%). Yellow solid. M.p. 109–111°. IR (KBr): 3430, 2115, 1575, 1525, 1491, 1358, 1160. 1H -NMR: 1.15 (t, $J = 6.2$, Me); 1.75–1.83 (m, CH_2); 2.68 (t, $J = 6.8$, CH_2); 6.94 (t, $J = 7.6$, 1 arom. H); 7.22 (d, $J = 7.6$, 2 arom. H); 7.33 (t, $J = 7.6$, 2 arom. H); 7.44 (d, $J = 8.0$, 2 arom. H); 7.95 (d, $J = 8.0$, 2 arom. H); 8.65 (s, NH). ^{13}C -NMR: 13.7 (Me); 21.8 (CH_2); 22.1 (CH_2); 71.3 (C); 105.7 (C); 113.5 (2 CH); 120.7 (CH); 125.7 (2 CH); 127.5 (C); 128.4 (2 CH); 128.6 (C); 128.9 (2 CH); 136.2 (C); 143.9 (C). MS: 296 (20, M^+), 253 (12), 219 (33), 111

(100), 77 (66), 67 (45), 43 (21). Anal. calc. for $C_{18}H_{17}N_2Cl$ (296.11): C 72.84, H 5.77, N 9.44; found: C 72.99, H 5.70, N 9.39.

1-[1-(4-Chlorophenyl)hept-2-yn-1-ylidene]-2-phenylhydrazine (3i). Yield: 0.22 g (72%). Yellow solid. M.p. 105–107°. IR (KBr): 3222, 2119, 1525, 1506, 1468, 1343, 1152. 1H -NMR: 1.17 (*t*, $J = 6.2$, Me); 1.26–1.36 (*m*, CH_2); 1.76–1.84 (*m*, CH_2); 2.65 (*t*, $J = 6.8$, CH_2); 6.95 (*t*, $J = 7.6$, 1 arom. H); 7.24 (*d*, $J = 7.6$, 2 arom. H); 7.34 (*t*, $J = 7.6$, 2 arom. H); 7.43 (*d*, $J = 8.0$, 2 arom. H); 7.98 (*d*, $J = 8.0$, 2 arom. H); 8.66 (*s*, NH). ^{13}C -NMR: 13.7 (Me); 20.0 (CH_2); 21.8 (CH_2); 22.2 (CH_2); 71.4 (C); 105.7 (C); 113.0 (2 CH); 120.7 (CH); 126.4 (2 CH); 127.2 (C); 128.5 (2 CH); 128.7 (C); 128.9 (2 CH); 136.1 (C); 143.5 (C). MS: 310 (15, M^+), 253 (55), 111 (67), 92 (100), 81 (44), 77 (55), 57 (45). Anal. calc. for $C_{19}H_{19}N_2Cl$ (310.12): C 73.42, H 6.16, N 11.41; found: C 73.67, H 6.21, N 11.47.

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Received November 28, 2013