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Palladium-catalyzed cycloisomerization of (*Z*)-(2-en-4-ynyl)amines: a new synthesis of substituted pyrroles

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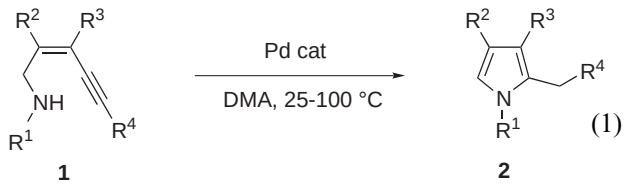
Abstract—(*Z*)-(2-En-4-ynyl)amines **1** bearing an internal triple bond undergo smooth cycloisomerization into pyrroles **2** in the presence of catalytic amounts of $PdCl_2$ in conjunction with KCl at 25–100°C in anhydrous *N*,*N*-dimethylacetamide. When the triple bond is terminal, spontaneous uncatalyzed cyclization to the corresponding pyrroles takes place.

We recently described a new approach to the construction of the furan or thiophene ring via Pd(II)-catalyzed cycloisomerization of (*Z*)-en-4-yn-1-ols[1] or (*Z*)-2-en-4-yne-1-thiols,[2] respectively. We now wish to report a useful extension of this methodology to the synthesis of substituted pyrroles[3] starting from readily available[†] (*Z*)-(2-en-4-ynyl)amines **1**, according to Eq. (1).

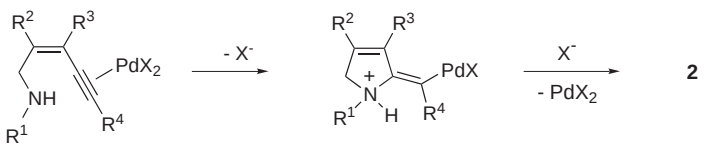


(1)

Table 1. Synthesis of pyrroles **2** by cycloisomerization of (*Z*)-(2-en-4-ynyl)amines **1** (1 equiv.) in anhydrous *N*,*N*-dimethylacetamide (DMA) in the presence of $PdCl_2$ (0.01 equiv.) and KCl (0.02 equiv.), substrate conc.: 2 mmol/mL DMA

Run	1	R^1	R^2	R^3	R^4	*T* (°C)	*t* (h)	Yield of **2** (%)[a]
1	**1a**	Bn	H	Me	Bu	100	6	60 (53)
2	**1b**	H	H	Me	Bu	100	6	75 (69)
3	**1c**	Bn	Et	H	Bu	25	6	94 (85)
4	**1d**	Bu	Ph	H	Bu	25	4	93 (86)

[a] GLC yield (isolated yield) based on starting **1**. Substrate conversion was practically quantitative in all cases.



Scheme 1.

Keywords: cycloisomerization; enynamines; palladium; pyrroles.

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† Starting **1** (R^1 = alkyl) were readily prepared in 50–80% yields from the corresponding (*Z*)-2-en-4-yn-1-ols[1] through bromination with PBr_3 in the presence of pyridine in Et_2O at −20°C, followed by nucleophilic substitution with a primary amine in DMF–EtOH at −15 to −10°C under the conditions described in Ref. 4. Substrates with R^1 = H were prepared from the corresponding (*Z*)-2-en-4-yn-1-ols[1] by reaction with phthalimide via a Mitsunobu reaction[5] in THF at 25°C, followed by cleavage with hydrazine in refluxing methanol under the conditions described in Ref. 6.

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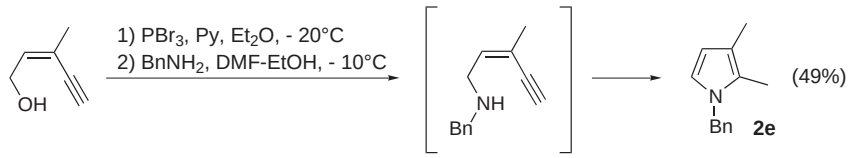

Scheme 2.

Representative results for enynamines bearing an internal triple bond are collected in Table 1. In a typical experiment, $PdCl_2$ (11 mg, 0.06 mmol) and KCl (9 mg, 0.12 mmol) were added under nitrogen to a solution of **1** (6 mmol) in anhydrous *N*,*N*-dimethylacetamide (DMA)[‡] (3 mL) in a Schlenk flask. The resulting mixture was stirred under nitrogen for the time required to obtain a satisfactory conversion, as shown by GLC and/or TLC analysis (Table 1). After addition of Et_2O, the mixture was filtered from the catalyst, washed with water and dried over Na_2SO_4. The solvent was removed in vacuo, and products were purified by column chromatography (SiO_2 or neutral Al_2O_3) using appropriate hexane–ethyl acetate mixtures as eluent.

The cycloisomerization process of **1a–d** did not occur in the absence of catalyst, as shown by blank experiments. The use of PdI_2+2KI led to comparable results with respect to $PdCl_2$+2KCl, in terms of reaction times as well as product yields. This is in contrast to that previously observed in the cycloisomerization of (*Z*)-2-en-4-yn-1-ols and (*Z*)-2-en-4-yne-1-thiols to furans[1] and thiophenes,[2] for which PdI_2+2KI proved to be a more active catalyst.

From the data reported in Table 1 it is evident that (*Z*)-(2-en-4-ynyl)amines substituted at C-2 and unsubstituted at C-3 (entries 3–4) are considerably more reactive than the analogous ones substituted at C-3 (entries 1–2). This result suggests that the triple bond coordinates to Pd(II) from the opposite side with respect to the -CH_2NHR[1] moiety; in fact, such a coordination is expected to be more favored in the absence of a substituent at C-3 for steric reasons. The activated triple bond then undergoes intramolecular 5-*exo*-*dig* nucleophilic attack by the nitrogen, the catalytic cycle being completed by protonolysis and aromatization or vice versa (Scheme 1, X = Cl, I; anionic halide ligands are omitted for clarity).

(*Z*)-(En-4-ynyl)amines bearing a terminal triple bond turned out to be unstable and spontaneously underwent cycloisomerization to the corresponding pyrroles. Thus, bromination of (*Z*)-3-methylpent-2-en-4-yn-1-ol followed by reaction with benzylamine directly afforded 1-benzyl-2,3-dimethylpyrrole **2e** in 49% isolated yield based on the starting enynol (Scheme 2).[§]

The reaction reported here is the first example of the synthesis of pyrroles by a Pd-catalyzed cycloisomerization of (*Z*)-(2-en-4ynyl)-1-amines. Pyrroles are a very important class of heterocyclic compounds which are widespread in Nature and find various significant applications.[8]

[‡] DMA was dried over 4 Å molecular sieves and distilled under nitrogen before use.

[§] 1-Benzyl-2,3-dimethylpyrrole **2e** was characterized by comparison with literature data.[7] All new pyrroles were fully characterized by IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. Spectroscopic and MS data of new compounds: Compound **2a**, yellow oil: IR (neat) 2954 (s), 2927 (s), 2857 (m), 1490 (m), 1453 (m), 1382 (w), 1354 (w), 1333 (m), 726 (m), 698 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.17 (m, 3H on phenyl ring), 7.01–6.95 (m, 2H on phenyl ring), 6.49 (d, J=2.9, 1H, H-5), 5.98 (d, J=2.9, 1H, H-4), 4.97 (s, 2H, NCH_2), 2.43 (t, J=7.6, 2H, =CCH_2CH_2), 2.05 (s, 3H, =CCH_3), 1.39–1.17 (m, 6H, $CH_2CH_2CH_2CH_3$), 0.85–0.79 (m, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.10, 129.76, 128.61, 127.24, 126.45, 119.45, 115.23, 108.80, 50.53, 31.64, 29.86, 24.34, 22.44, 13.95, 11.59; MS *m*/*e* 241 (M^+, 23), 185 (17), 184 (100), 92 (7), 91 (70), 65 (10). Compound **2b**, yellow oil: IR (neat) 3383 (s), 2955 (m), 2927 (m), 2856 (m), 1463 (w), 713 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (br s, 1H, NH), 6.52–6.48 (m, 1H, H-5), 5.99–5.94 (m, 1H, H-4), 2.48 (t, J=7.6, 2H, =CCH_2), 2.02 (s, 3H, =CCH_3), 1.58–1.44 (m, 2H, =$CCH_2CH_2CH_2$), 1.39–1.20 (m, 4H, $CH_2CH_2CH_2CH_3$), 0.89 (t, J=6.9, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.40, 114.70, 113.54, 109.82, 31.50, 29.81, 25.72, 22.39, 13.87, 10.74; MS *m*/*e* 151 (M^+, 17), 95 (7), 94 (100). Compound **2c**, yellow oil: IR (neat) 2958 (s), 2929 (s), 2869 (m), 1454 (m), 1354 (w), cm^{-1}; ^1H NMR δ 7.29–7.14 (m, 3H on phenyl ring), 7.00–6.93 (m, 2H on phenyl ring), 6.36–6.33 (m, 1H, H-5), 5.85–5.81 (m, 1H, H-3), 4.91 (s, 2H, CH_2Ph), 2.52–2.43, (m, 2H, =CCH_2CH_3), 2.42–2.35 (m, 2H, =CCH_2CH_2), 1.61–1.48 (m, 2H, =CCH_2CH_2), 1.34–1.23 (m, 4H, $CH_2CH_2CH_3$), 1.80 (t, J=7.5, 3H, =CCH_2CH_3), 0.89–0.82 (m, 3H, $CH_2CH_2CH_3$); ^{13}C NMR δ 139.87, 133.40, 128.50, 127.06, 126.33, 125.10, 117.21, 105.85, 49.92, 31.61, 28.53, 26.04, 22.38, 20.16, 15.17, 13.85; MS *m*/*e* 255 (M^+, 22), 199 (20), 198 (69), 92 (9), 91 (100), 65 (11). Compound **2d**, yellow oil: IR (neat) 2956 (s), 2929 (s), 2869 (m), 1604 (m), 1521 (m), 1455 (m), 1367 (m), 1206 (m), 757 (m), 694 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H on phenyl ring), 7.32–7.25 (m, 2H on phenyl ring), 7.14–7.07 (m, 1H on phenyl ring), 6.87 (d, J=2.0, 1H, H-5), 6.19 (dt, J=2.0, 1.0, 1H, H-3), 3.79 (t, J=7.3, 2H, NCH_2), 2.53 (td, J=7.8, 1.0, 2H, =CCH_2), 1.78–1.63 (m, 4H, NCH_2CH_2+=CCH_2CH_2), 1.47–1.30 (m, 6H, $NCH_2CH_2CH_2CH_3$+$CH_2CH_2CH_2CH_2CH_3$), 0.95 (t, J=7.3, 3H, CH_3), 0.95–0.89 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.38, 134.35, 128.49, 124.91, 124.81, 123.27, 116.48, 103.60, 46.34, 33.56, 31.80, 28.71, 26.28, 22.58, 20.08, 14.03, 13.75; MS *m*/*e* 269 (M^+, 65), 227 (7), 226 (28), 213 (29), 212 (100), 198 (30), 185 (7), 184 (26), 182 (9), 171 (36), 170 (61), 169 (8), 168 (7), 157 (13), 156 (33), 129 (11), 128 (25), 127 (11), 115 (12). Elemental analyses were satisfactory for all compounds.

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