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Mendeleev Commun., 2019, **29**, 252–253

Mendeleev Communications

Copper(I) halide-promoted formation of 3-acyl-5-halopyridine moiety from NH-2-(2-acylethynyl)pyrroles and propargylamine

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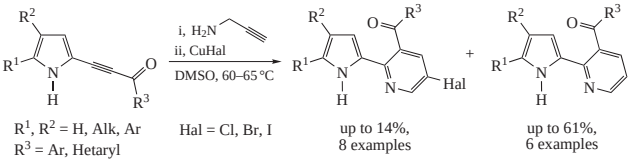
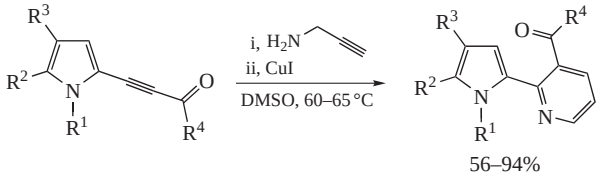
DOI: 10.1016/j.mencom.2019.05.003

Available NH-2-acylethynylpyrroles undergo annulation/aromatization with propargylamine in the presence of 1 equiv. of CuHal (Hal = Cl, Br, I) at 60–65 °C to afford 3-acyl-2-(pyrrol-2-yl)pyridines and their 5-halo analogues in 28–61 and 5–14% yields, respectively. The latter are assumed to be resulted from halohydrogenation of the intermediate Cu-pyrrolylpropargyl amino enones.



Pyrrole–pyridine ensembles that combine two important heterocyclic scaffolds closely relate to life-sustaining natural systems and are regarded as privileged objects for drug design[1–6] and advanced materials science.[7–11] Among their most efficient syntheses is the annulation/aromatization of N-substituted 2-acylethynylpyrroles with propargylamine in the presence of CuI published recently[12] (Scheme 1). The starting 2-acylethynylpyrroles became available *via* metal-free cross-coupling of pyrroles with acylhaloacetylenes in solid alumina.[13–15] The accessibility of the starting materials makes this synthesis particularly attractive and justifies its further development.



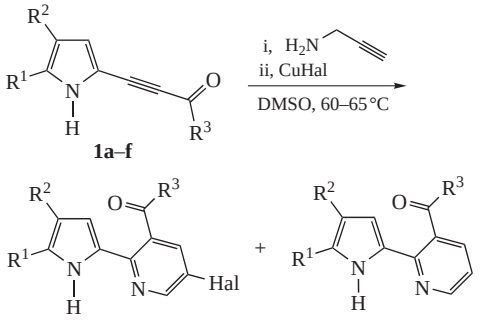
R^1 = Me, Bn, vinyl
R^2 = Me, Ph, 4-FC_6H_4, 4-ClC_6H_4
R^3 = H
$R^2 + R^3 = (CH_2)_4$
R^4 = Ph, 2-furyl, 2-thienyl

Scheme 1

Here we report on the peculiarity of the aforementioned reaction, which is observed when instead of N-substituted 2-acylethynylpyrroles, their NH congeners **1a–f** have been employed. In this case, unexpected 5-halo analogues **2a–f**, **2′d**, **2′′d**, **2′f**, **2′′f** along with anticipated non-halogenated ones **3a–f** are formed (Scheme 2).

The synthesis has been implemented as a one-pot two-step process, first, the catalyst-free addition of propargylamine to 2-acylethynylpyrroles **1** in DMSO at 60–65 °C for 6–15 h, dependent on the substituent nature and, second, the cyclization/aromatization of the intermediate *N*-propargyl-*N*-pyrrolylamino enones **A** (Scheme 3) after addition of 1 equiv. of copper(I) halide at the same temperature and heating the mixture for more 2.5 h. The halogenated (**2**) and non-halogenated (**3**) pyrrolylpyridines are easily separated by column chromatography.†

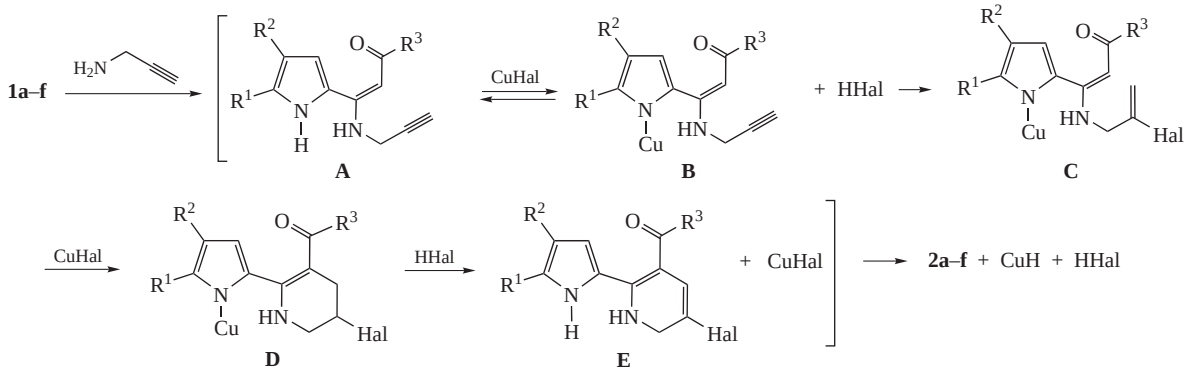
Under the above conditions, pyrrolylpyridines **3** are not halogenated with CuHal thus indicating that introduction of the halogen occurs before closure of the pyridine ring. Apparently,



	R^1	R^2	R^3	Hal	Yield of **2** (%)	Yield of **3** (%)
a	H	H	Ph	I	9	61
b	$(CH_2)_4$		Ph	I	0	28
c	Ph	H	Ph	I	12	48
d	4-FC_6H_4	H	Ph	I	8	30–40
d′	4-FC_6H_4	H	Ph	Br	5	
d′′	4-FC_6H_4	H	Ph	Cl	8	
e	4-FC_6H_4	H	2-furyl	I	0	38
f	4-ClC_6H_4	H	Ph	I	9	28–42
f′	4-ClC_6H_4	H	Ph	Br	14	
f′′	4-ClC_6H_4	H	Ph	Cl	6	

Scheme 2 *Reagents and conditions*: i, ynone **1a–f** (1 mmol), propargylamine (2 mmol), DMSO (7–10 ml), 60–65 °C, ~6 h (for **1b**, 15 h); ii, CuHal (1 equiv.), 60–65 °C, ~2.5 h (**2′d** not isolated in pure state).

† *Synthesis of compounds* **2**, **3** *(typical procedure)*. A solution of 2-acylethynylpyrrole **1a–f** (1 mmol) and propargylamine (2 mmol) in DMSO (7–10 ml) was heated at 60–65 °C for 6–15 h until the signals of 2-acylethynylpyrrole **1a–f** disappeared. Then CuHal (1 mmol) was added and the mixture was heated at 60–65 °C for 2.5 h. After cooling to room temperature, the mixture was diluted with brine (1 : 10) and the precipitate formed was filtered off, washed with H_2O (5 × 15 ml), dried over K_2CO_3 and fractionated by column chromatography (Al_2O_3, hexane–diethyl ether, 3 : 1) to elute first 5-halo-2-pyrrolylpyridines **2** and then pyrrolylpyridines **3**.



Scheme 3

hydrogen halides (reversibly generated by the interaction of the NH pyrrole moiety of the intermediate *N*-propargyl-*N*-pyrrolylamino enone **A** with CuHal) add at the triple bond activated by π-complexing with other CuHal molecules to give haloallyl intermediate **C** (see Scheme 3). Afterwards, the intramolecular addition of the CH bond to the allyl moiety takes place to form the intermediate 5-halotetrahydropyridine intermediate **D**. Aromatization of the intermediate **E** is finalized *via* the reaction with CuHal and further oxidation with Cu^+ cations as previously described for a similar process.[12] Certainly, the aromatization of the intermediate halodihydropyridine **E** procceds mainly as the thermodynamically favorable elimination of hydrogen halides to afford non-halogenated pyridine moiety. The dehydrogenation of this intermediate **E** occurs as a minor parallel reaction.

To summarize, in view of poor availability of 5-halo-2-(pyrrol-2-yl)pyridines **2**, our results seem promising for wider study of these compounds despite modest isolated yields herein achieved.

The main results were obtained using the equipment of the Baikal Analytical Center for Collective Use, Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.003.

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Received: 19th November 2018; Com. 18/5743

*[5-Iodo-2-(1*H*-pyrrol-2-yl)pyridin-3-yl](phenyl)methanone* **2a**. Yield 0.034 g (9%), yellow crystals, mp 130–132 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 9.65 (br. s, 1H, NH), 8.78 (d, 1H, H-6 pyridine, *J* 2.0 Hz), 7.86–7.84 (m, 2H, H-2,6 COPh), 7.82 (d, 1H, H-4 pyridine, *J* 2.0 Hz), 7.62–7.58 (m, 1H, H-4 COPh), 7.47–7.43 (m, 2 H, H-3,5 COPh), 6.85–6.84 (m, 1H, H-5 pyrrole), 6.24–6.22 (m, 1H, H-3 pyrrole), 6.08–6.06 (m, 1H, H-4 pyrrole). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 195.8 (C=O), 155.6 (C-6 pyridine), 145.9 (C-2 pyridine), 143.2 (C-4 pyridine), 136.0 (C-1 COPh), 134.4 (C-4 COPh), 132.5 (C-3 pyridine), 130.2 (C-2,6 COPh), 129.0 (C-3,5 COPh), 128.3 (C-2 pyrrole), 120.7 (C-5 pyrrole), 112.5 (C-3 pyrrole), 111.1 (C-4 pyrrole), 87.0 (C-5 pyridine). IR (KBr, ν/cm^{-1}): 3430, 3115, 3058, 2923, 2854, 2550, 1666, 1590, 1559, 1534, 1452, 1431, 1378, 1311, 1275, 1214, 1178, 1104, 1047, 945, 796, 733, 683, 644, 593, 457. Found (%): C, 51.23; H, 2.88; I, 33.71; N, 7.54. Calc. for $C_{16}H_{11}IN_2O$: C, 51.36; H, 2.96; I, 33.92; N, 7.49.

*(Phenyl)[2-(1*H*-pyrrol-2-yl)pyridin-3-yl]methanone* **3a**. Yield 0.151 g (61%), yellow crystals, mp 111–112 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 9.76 (br. s, 1H, NH), 8.61 (dd, 1H, H-6 pyridine, *J* 4.7 Hz, *J* 1.4 Hz), 7.86–7.84 (m, 2H, H-2,6 COPh), 7.59–7.54 (m, 2 H, H-4 pyridine, H-4 COPh), 7.45–7.41 (m, 2 H, H-3,5 COPh), 7.15 (dd, 1H, H-5 pyridine, *J* 7.6, 4.7 Hz,), 6.84–6.83 (m, 1H, H-5 pyrrole), 6.28–6.26 (m, 1H, H-3 pyrrole), 6.09–6.07 (m, 1H, H-4 pyrrole). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 197.5 (C=O), 149.8 (C-6 pyridine), 147.2 (C-2 pyridine), 136.5 (C-1 COPh), 135.9 (C-4 pyridine), 134.0 (C-4 COPh), 131.1 (C-3 pyridine), 130.2 (C-2,6 COPh), 129.2 (C-2 pyrrole), 128.8 (C-3,5 COPh), 120.2 (C-5 pyrrole), 119.5 (C-5 pyridine), 111.9 (C-4 pyrrole), 110.7 (C-3 pyrrole). IR (KBr, ν/cm^{-1}): 3435, 3249, 3068, 2923, 2855, 2158, 1740, 1666, 1569, 1445, 1313, 1277, 1227, 1151, 1129, 1095, 1045, 929, 878, 790, 742, 710, 639, 599, 425. Found (%): C, 77.54; H, 4.77; N, 11.18. Calc. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28;

For characteristics of compounds **2b**–**f**, **2′d**, **2′′d**, **2′e**, **2′′e**, and **3b**–**f**, see Online Supplementary Materials.