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Aluminium oxide-mediated cross-coupling of pyrroles with 1-bromo-2-(trifluoroacetyl)acetylene: a quantum-chemical insight

Denis N. Tomilin,[a] Dmitri Yu. Soshnikov,[a,b] Alexander B. Trofimov,[b] Maxim D. Gotsko,[a] Lyubov N. Sobenina,[a] Igor A. Ushakov,[a] Andrey V. Afonin,[a] Andrey B. Koldobsky,[c] Nadezhda M. Vitkovskaya[b] and Boris A. Trofimov*[a]

[a] *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 419 346; e-mail: boris_trofimov@irioch.irk.ru*
[b] *Laboratory of Quantum Chemistry, Irkutsk State University, 664003 Irkutsk, Russian Federation*
[c] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

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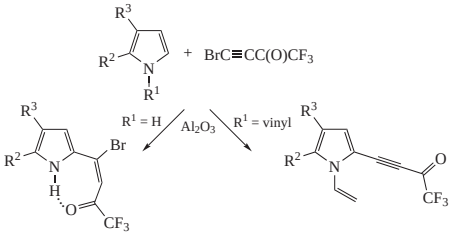
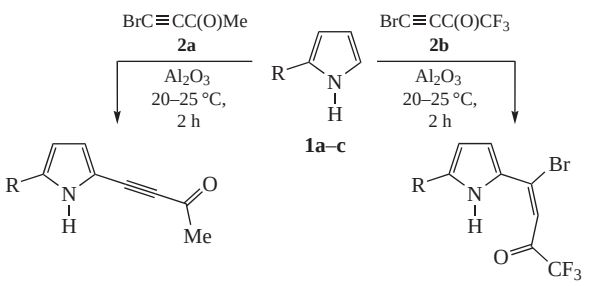
Cross-coupling of NH-pyrroles with 1-bromo-2-(trifluoroacetyl)acetylene in the Al_2O_3 medium affords (*E*)-4-bromo-1,1,1-trifluoro-4-(pyrrol-2-yl)but-3-en-2-ones instead of the expected 2-ethynylated products. Quantum-chemical analysis shows strong intramolecular hydrogen bonding between NH and trifluoroacetyl groups, higher NH acidity and deeper charge transfer to the ethenyl moiety, which determines the reaction pathway.



The transition metal- and solvent-free cross-coupling of pyrroles[1,2] and indoles[3,4] with functionalized electron-deficient haloacetylenes in solid metal oxides and salts attracts a considerable attention[5–9] owing to efficiency, mild conditions (room temperature) and simplicity of the experimental protocol. This reaction proved to be an essential complement to the Sonogashira coupling which is known as ineffective for functionalized acetylenes with electron-withdrawing substituents,[10] whereas the starting halopyrroles are poorly accessible and unstable.[11,12] Recently,[9] even higher reactive halodiacetylenes with electron-deficient functions have been shown to tolerate these reaction conditions.

Surprisingly, 1-bromo-1,1,1-trifluorobut-3-yn-2-one, when introduced in this cross-coupling, has been found to behave unusually, which might shed an additional light on the reaction mechanism. This communication briefly describes this observation and its quantum-chemical analysis.

In fact, NH-pyrroles **1a–c** are cross-coupled with unfluorinated analogue **2a** in the solid Al_2O_3 medium (the reactants were ground intensively with 10-fold mass excess of solid Al_2O_3 for 5–10 min and the reaction mixture was allowed to stand at room temperature on air for 1 h) to give the expected acetylethynylpyrroles **3a–c**. Meanwhile, its trifluoroacetyl analogue **2b** was transformed into 4-bromo-1,1,1-trifluoro-4-(pyrrol-2-yl)but-3-en-2-ones **4a–c** only, though in lower yields (Scheme 1).†

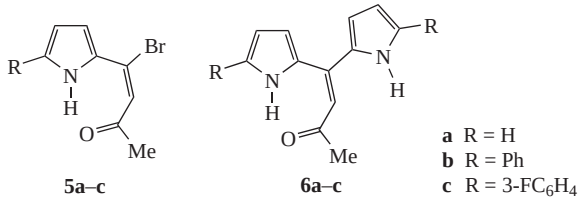


3a R = H (30%)
3b R = Ph (38%)
3c R = 3-FC_6H_4 (55%)

4a R = H (21%)
4b R = Ph (17%)
4c R = 3-FC_6H_4 (12%)

Scheme 1

When the reaction was carried out with acetylene **2a** for 1 h, the reaction mixture contained, along with acetylethynylpyrroles **3a–c**, considerable amounts of the corresponding 4-bromo-4-(pyrrol-2-yl)but-3-en-2-ones **5a–c** and 4,4-di(pyrrol-2-yl)but-3-en-2-ones **6a–c** (Table 1). They were identified in NMR spectra of the reaction mixtures by characteristic signals of the NH groups (13.38–14.30 ppm for compounds **5a–c**, 14.20–14.56 ppm and 8.20–8.91 ppm for compounds **6a–c**) and protons at the double bonds (6.63–6.67 ppm for compounds **5a–c** and 6.54–6.63 ppm for compounds **6a–c**).



5a–c **6a–c**

a R = H
b R = Ph
c R = 3-FC_6H_4

Compounds **5a–c**, **6a–c** are almost completely decomposed during their isolation after removing the extractant.

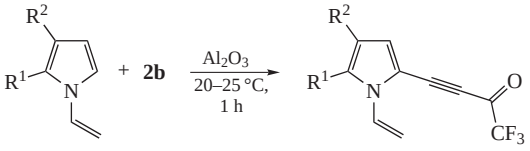
As seen from Table 1, conversion of the starting pyrroles **1b**,**c** is about 80%. Notably, with trifluoro analogue **2b**, the coupling is completed within 1 h under the same conditions thus confirming the expected higher reactivity of this acetylene.

Importantly, *N*-vinylpyrroles **1d–f** undergo normal cross-coupling with alkyne **2b** to deliver etnynylpyrroles **3d–f** in 42–58% yields (Scheme 2).

† For experimental procedures and details of quantum-chemical calculations, see Online Supplementary Materials.

Table 1 Products ratio (^{1}H NMR) of the reaction between pyrroles **1a–c** and 4-bromobut-3-yn-2-one **2a** (Al_2O_3, 20–25 °C, 1 h).

Compound	Content (%)	Compound	Content (%)	Compound	Content (%)
1a	0	**1b**	22	**1c**	19
3a	54	**3b**	54	**3c**	65
5a	32	**5b**	22	**5c**	13
6a	14	**6b**	2	**6c**	3



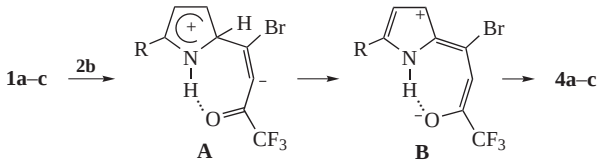
1d–f **3d–f**

d R^1 = Ph, R^2 = H (58%)
e R^1 = 3-FC_6H_4, R^2 = H (42%)
f $R^1 + R^2 = (CH_2)_4$ (48%)

Scheme 2

This implies that the cause of abnormal reaction (see Scheme 1) is the interaction between NH and trifluoroacetyl groups that stabilizes the products **4a–c**.

Indeed, the extraordinary downfield position of the NH group proton signal (13–14 ppm) in the ^{1}H NMR spectra of pyrroles **4a–c** evidences the strong N–H···O intramolecular hydrogen bonding in the energetically favorable *E*-configuration (Scheme 3).



Scheme 3

Additionally, the ^{15}N–^{1}H coupling constant across the N–H bond as well as the ^{1}H–^{1}H coupling constant between the pyrrole ring protons and the proton of the NH group ($^1J_{NH}$ 94 Hz and $^4J_{HH}$ 2.5 Hz) are in agreement with such an interaction, which are indicative of the keto form of compounds **4a–c**. Further support for this rationale follows from only single minimum found by MP2/cc-pVTZ calculations on the potential energy surface of **4a** that corresponds to its keto form (Figure 1). No H-bound enol form of **4a** is predicted by the calculations. The hydrogen transfer from nitrogen to oxygen (along approximate reaction coordinate expressed in terms of the HO distance) is characterized by steady increase of energy reaching 9.9 kcal mol^{-1} at R_{HO} = 1.05 Å, where the molecule can be considered to be in a hypothetical enol form (Figure S3, see Online Supplementary Materials).

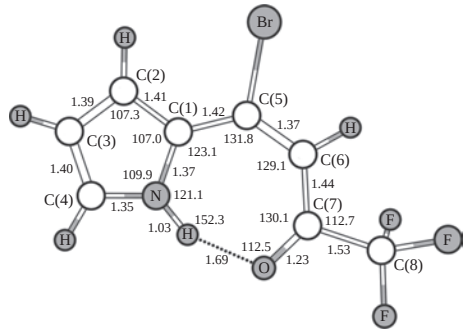


Figure 1 Schematic representation of pyrrole **4a** showing geometrical parameters calculated at the MP2/cc-pVTZ level of theory.

More directly, the H···O bond is proved by the AIM calculations, which find bond critical point [BCP(3,–1)] within the H···O domain and the seven-membered chelate ring H–N–C(1)–C(5)–C(6)–C(7)–O (Figure 1), as follows from the identified ring critical point [RCP(3,+1)]. The H···O bond energy estimated by approximate theoretical framework[13] is 16.8 kcal mol^{-1}, so that the bond should be classified as strong. According to the calculated values of the AIM characteristics (electron density, electron density Laplacian, and electron energy density) at BCP(3,–1), the H···O bond is of an intermediate ionic/covalent type with pronounced covalent contribution (Table S4, Online Supplementary Materials). The covalent character of the H···O bond is also supported by the presently calculated energy of the NBO donor–acceptor interaction of the oxygen lone pairs (LP) with the σ-type N–H antibonding orbital ($O_{LP} \rightarrow \sigma^*_{NH}$) of 21.4 and 9.4 kcal mol^{-1} for the LPs oriented collinearly and perpendicularly to the C=O bond, respectively. The ionic (electrostatic) component of the H···O bond is notably influenced by the CF_3 group. Expectedly, as follows from the calculations for **4a** and its CF_3/Me-substituted analogue **5a**, the CF_3 group has more negative I-effect compared to the Me group, which can be seen from the smaller negative charge on the oxygen atom, larger H···O distance and weaker H···O bonding in the former case (Figures 1, S1, S2, Tables S1–S4).

Similarly, intramolecular hydrogen bond may be implied in the intermediate zwitterion **A**, which also stabilizes the *E*-form (Scheme 3). This hydrogen bonding should prevent the *E* ↔ *Z* isomerization and hence elimination of HBr, which usually occurs as a *trans*-process. Notably, in most previous examples of ethynylation of pyrroles or indoles under similar conditions,[1,3,6,8] ethenylpyrroles of the type **4a–c** were formed just as minor contaminants (0–10% yields), which also may be a result of easier elimination of hydrogen halides (HBr in this case) from their *Z*-isomers. As the elimination of HBr does not occur at a stage of the zwitterion **A** formation, the 2-positioned proton of pyrrole ring is transferred to the carbanionic center facilitated by a strong electron-withdrawing effect of trifluoroacetyl substituent. Thus, the end product **4a–c** is formed solely as the *E*-form.

Note that significant contribution of the zwitterionic structure **B** to the ground state of the final pyrroles **4a–c** (Scheme 3) follows from a considerable deshielding of the pyrrole ring C(2) carbon (Figure 1) by 19–22 ppm with respect to the parent pyrrole and shielding of the butenone moiety C_β carbon [C(6) in Figure 1] by 13–14 ppm with respect to the ethylene. These observations are in excellent agreement with the calculated NBO atomic charges in Table 2.

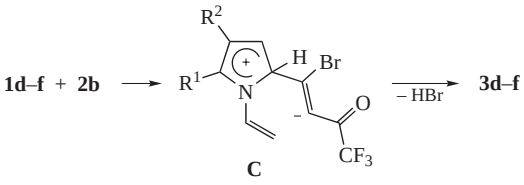
Thus, the final stage of the reaction of 1*H*-pyrroles **1a–c** with trifluoro compound **2b** may be considered in some sense as the transformation of the zwitterion **A** to the zwitterion **B** (see Scheme 3).

Upon reaction of *N*-vinylpyrroles **1d–f** with the acetylene **2b**, the formation of an intramolecular hydrogen bond in the reaction products is impossible (Scheme 4). Moreover, the formation of the *E*-form of intermediate **C** would be sterically hindered due to the repulsion between *N*-vinyl group and trifluoroacetyl substituent.

Table 2 Atomic charges (in electron units) calculated using NBO approach at the HF/cc-pVDZ level of theory for pyrrole **4a** in comparison with the charges in pyrrole and ethylene.[a]

Molecule	H	N	C(1)	C(2)	C(5)	C(6)	C(7)	O
4a	0.49	–0.61	0.02	–0.18	0.07	–0.48	0.57	–0.68
Unsubstituted pyrrole	0.41	–0.63	–0.01	–0.32				
Ethylene					–0.39	–0.39		

[a] Atoms are numbered as shown in Figure 1.



Scheme 4

Despite the approximately equal strength of the intramolecular hydrogen bond in **5a** and **4a** (18.23 and 16.83 kcal mol^{-1}), ethynylpyrrole **3a** is still formed. Therefore, this interaction is not the only cause of the selective formation of ethenylpyrroles **4a**–**c**. Apparently, in the cross-coupling of pyrroles with **2b**, a stronger charge transfer in the zwitterion **A** and a higher NH acidity are also important: the former prevents the earlier elimination of Br^-, and the latter facilitates neutralization of the carbanionic center additionally slowing down HBr elimination.

In addition, one should not neglect the fact that reaction **2a** + **1a**–**c** gives minor ethenylpyrroles **5a**–**c** in almost the same quantities (see Table 1) as ethenylpyrroles **4a**–**c**.

To summarize, the unusual regioselective formation of 4-bromo-1,1,1-trifluoro-4-(pyrrol-2-yl)but-3-en-2-ones from NH-pyrroles and bromotrifluoroacetylacetylene in the Al_2O_3 medium, instead of expected 2-trifuoroacetylethynylpyrroles, has been subjected to quantum-chemical analysis. This reaction way can result from a strong intramolecular H-bonding between NH and O=C moieties, higher NH acidity and deeper charge transfer from the pyrrole ring to the unsaturated parts of the molecule. These results provide additional evidences for zwitterionic mechanism of the interaction between pyrroles and halogenated electron-deficient acetylenes.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.11.006.

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