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A facile synthesis of 2-ethynylpyrroles by Bu^{t}OK-assisted room temperature deprotection of 2-(acylethynyl)pyrroles

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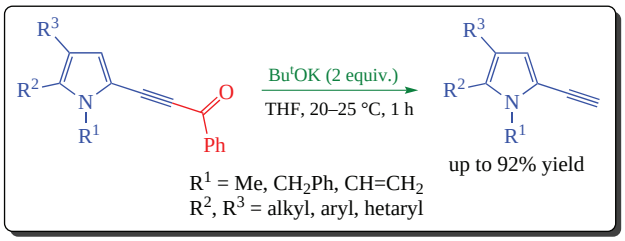
Available *N*-substituted 2-(acylethynyl)pyrroles undergo room temperature deprotection in the Bu^{t}OK/THF system to give 2-ethynylpyrroles in 82–92% yields. Quantum-chemical calculations (B2PLYP/6-311G//B3LYP/6-311G**+C-PCM/THF) show that the cleavage of ethynyl–acyl bond *via* the proton transfer from Bu^{t}OK with formation of potassium acylate and 2-methylpropene is thermodynamically much more preferred compared to alternative nucleophilic attack of *tert*-butoxide anion at the acyl carbon (Δ*G* = –35.1 *vs.* –2.7 kcal mol^{-1}).**



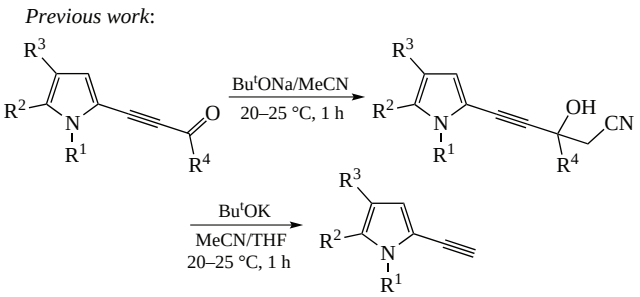
Keywords: (acylethynyl)pyrroles, ethynylpyrroles, terminal alkynes, deacylation, deprotection, ynones, pyrroles, potassium *tert*-butoxide.

Ethynylpyrroles are rewarding synthetic intermediates in the design of various drug-related and natural compounds, among which are antibiotic roseophilin, active against K562 human erythroid leukemia cells[1] and alkaloid insecticide quinolactacide.[2] These compounds are also employed in the syntheses of EGFR tyrosine kinase and HMG-CoA reductase inhibitors,[3] dopamine D4 receptor ligands,[4] and receptors for encapsulation of dihydrogenphosphate ions.[5] Terminal ethynylpyrroles are used for the construction of low-toxic BODIPY fluorophores with high quantum yields for biological applications.[6] They can be of interest for advanced materials science, *e.g.*, to devise the detectors of tetrahedral oxoanions ($H_2PO_4^-$ and SO_4^{2-})[7] and pyrophosphate anions.[8] Besides, these pyrrole/acetylene hybrids[9] find application in the design of ultrasensitive fluorescent probes,[10] photoswitchers,[11–13] solar cells[14] and thin-film transistors.[15]

Ethynylpyrroles can be synthesized by the cross-coupling of halopyrroles with acetylene compounds. The use of ethynylmagnesium chloride or ethynylzinc bromide in the Negishi reaction[16] or alkynes with easily removable groups, like TMS/TIPS, in the reaction with halopyrroles (the Sonogashira cross-coupling),[2,4,5,7,17–19] provides access to ethynylpyrroles with a terminal triple bond. The required halopyrroles are synthesized mostly by electrophilic halogenation of the pyrrole ring. However, due to low stability of halopyrroles[20] and complications in their preparation,[4,21–29] this approach is rather limited. Less frequent is the synthesis of ethynylpyrroles (~50% yields for two steps) *via* the reaction of pyrrolecarbaldehydes first with CBr_4/PPh_3 and then with Bu^{n}Li at –78 °C.[1,6,30–32]

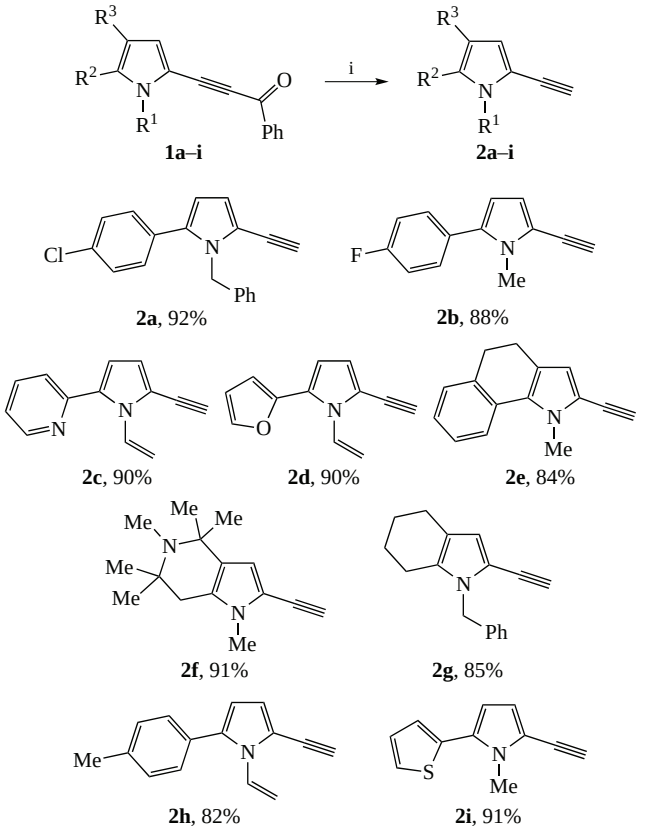
Recently,[33] we found that ethynylpyrroles could be synthesized by deprotection of 2-(acylethynyl)pyrroles with Bu^{t}OK in MeCN. That synthesis was experimentally proved to involve the *retro*-Favorsky decomposition of intermediate tertiary acetylenic alcohols, adducts of the cyanomethylene carbanion attack to the carbonyl group of 2-(acylethynyl)pyrroles (Scheme 1).

Since 2-(acylethynyl)pyrroles are now readily available from the room temperature cross-coupling of pyrroles with 1-acyl-2-bromoacetylenes in solid Al_2O_3,[34–38] the search for a direct and simpler procedure for their deprotection was justified. In this communication, we report that 2-(acylethynyl)pyrroles **1a–i** can be easily deprotected (room temperature, 1 h) under the action of Bu^{t}OK in THF to give directly, avoiding any intermediate, 2-ethynylpyrroles **2a–i** in high yields (Scheme 2).[†] Compounds



Scheme 1

[†] *General procedure for the synthesis of 2-ethynylpyrroles* **2a–i**. The appropriate 2-(acylethynyl)pyrrole **1a–i** (1 mmol) was dissolved in dry THF (4 ml) under a nitrogen atmosphere and then Bu^{t}OK (224 mg, 2 mmol) was added in portions. The reaction mixture was stirred at room temperature for 1 h, and during this time it turned into an orange

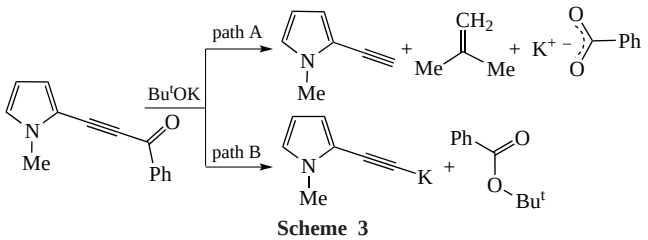


Scheme 2 *Reagents and conditions*: i, 2-(acylethynyl)pyrrole (1 mmol), Bu^{t}OK (2 mmol), THF (4 ml), nitrogen atmosphere, 20–25 °C, 1 h.

2a–**f** are new. The procedure thus developed allows not only ethynylpyrroles **2a**–**d**,**g**–**i** but also 2-ethynylbenzo[*g*]indole **2e** and 2-ethynylpyrrolo[3,2-*c*]pyridine **2f** to be efficiently synthesized. These results point out that the studied reaction may, in the long run, produce a wide substrate scope. Therefore, the present approach can be considered as a general strategy for the introduction of a terminal ethynyl moiety to the monocyclic pyrrole ring, and also to pyrrole annulated carbocyclic or heterocyclic systems.

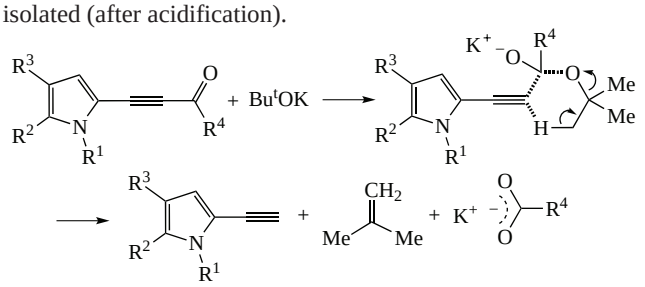
Mechanistically, the Bu^{t}OK-assisted deprotection of 2-(acylethynyl)pyrroles could proceed (Scheme 3) either as a cleavage of the bond between acetylenic and acyl moiety with the proton transfer from potassium *tert*-butoxide to form ethynylpyrroles, potassium carboxylate and 2-methylpropene (path A) or as the nucleophilic attack of *tert*-butoxide anion at the carbonyl group to give potassium derivatives of ethynylpyrroles and *tert*-butyl ester (path B).

To distinguish between these two mechanistic options, we have performed quantum-chemical calculations (B2PLYP/6-311G**//B3LYP/6-311G**+C-PCM/THF) of the Gibbs free energy change (ΔG) for both cases. As followed from the calculations, both reactions are thermodynamically feasible with ΔG = –35.1 and –2.7 kcal mol^{-1}, respectively, but path A is much more feasible than path B, since for the latter a significantly smaller exothermic effect was predicted (for details, see Online Supplementary Materials).



Scheme 3

The proton transfer (path A) may occur *via* the cyclic transition state in which the attack of *tert*-butoxide anion at the carbonyl group and the proton migration from *tert*-butyl to acetylenic moiety occur simultaneously (Scheme 4). Path B also should be rejected since nothing of *tert*-butyl benzoate was detected in the reaction mixture while instead benzoic acid was isolated (after acidification).



Scheme 4

From the proved mechanism (path A) it follows that a part of the base should be consumed for the formation of potassium derivative of ethynylpyrrole. Therefore, an excess of Bu^{t}OK is required for the process completion, so its 2-fold molar excess was employed. Otherwise (with equimolar ratio of the reactants) up 20% of the starting (acylethynyl)pyrrole remained unreacted.

In conclusion, we have found that 2-(acylethynyl)pyrroles are easily and directly, avoiding any intermediates, deacylated in Bu^{t}OK in THF (room temperature, 1 h) to afford free 2-ethynylpyrroles in high yields. In view of the starting 2-(acylethynyl)pyrroles accessibility (room temperature ethynylation of pyrroles with 1-acyl-2-bromoacetylenes), the reaction developed may be considered as a gate to the general strategy to access ethynylpyrroles, to be used as intermediates for design of drugs and high-tech materials.

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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.2023.06.005.

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suspension. The reaction mixture was then diluted with cold (0–5 °C) water (30 ml) and extracted with cold (0–5 °C) *n*-hexane (3×10 ml). The combined organic extracts were washed with water (3×5 ml) and dried over Na_2SO_4. The residue, after removing solvent, was purified by flash chromatography (dried SiO_2, *n*-hexane) to afford the corresponding 2-ethynylpyrroles **2a**–**i** in 82–92% yields.

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