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Acetylene based short route from 2,2,6,6-tetramethylpiperidin-4-one oxime to 2-(pyrazol-5-yl)-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridines

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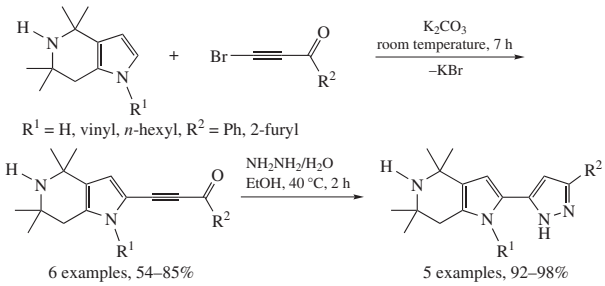
Pharmaceutically relevant substituted 2-(pyrazol-5-yl)-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridines have been assembled in good to excellent yields *via* the reaction of 2,2,6,6-tetramethylpiperidin-4-one oxime with acetylene, cross-coupling of the resulting 4,4,6,6-tetramethyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]-pyridines with aroylbromoacetylenes, and reaction of the formed 2-(aroylethynyl)-4,4,6,6-tetramethyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridines with hydrazine.



Natural and synthetic fused aromatic N-heterocycles are important motifs in the structures of natural products, drugs and advanced organic materials.[1] Pyrrolopyridines belong to this class of compounds,[2] and some of them represent kinase inhibitors due to the structural similarity to the purine ring of adenosine. The most successful pyrrolopyridine-derived drug currently used in the market is Vemurafenib, which is effective in the treatment of melanoma due to its selective inhibition action on V600E mutated B-Raf kinase.[2(a)] Representatives of pyrrolopyridines have been found to possess anticancer, antiviral, muscarinic antagonist and anti-Parkinson properties.[2(a)]

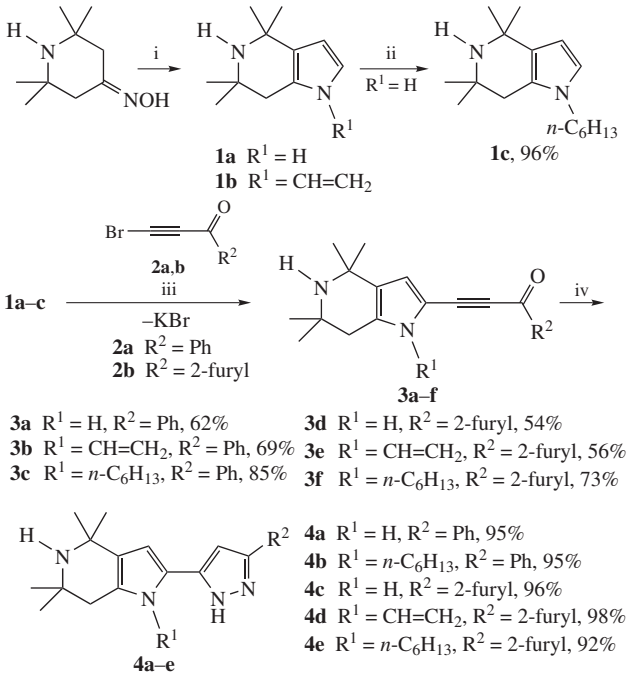
Within modern trends in medicinal chemistry, saturated heterocycles deserve special attention, since multiple sp^3 chiral centers lead in general to an additional chirality and an improved interaction with target proteins, thereby increasing the probability of finding a successful drug.[3] Besides, bonds saturation often correlates with solubility as a valuable property for the pharmaceuticals design.[3] Therefore, it is expected that hydrogenated pyrrolopyridines will exhibit prospective biological activity. As an illustration, the related scaffolds are known to be potential inhibitors of MK2 kinase,[4] Polo-like kinase 1[5] and cell division cycle 7 kinase[6] as well as antagonists of CB-1[7] and GnRH[8] receptors. They are also considered as potential drugs for the treatment of conditions like rheumatoid arthritis, inflammation, cancer, obesity, diabetes, Alzheimer's disease and mood disorders.[9] Hydrogenated pyrrolopyridines also demonstrate anti-hypertensive, anti-tremor[10] and platelet aggregation inhibition[11] effects, suppress appetite and induce weight loss.[12] Moreover, similar structures are proposed for the treatment of mental and neurological disorders.[13]

Although the hydrogenated pyrrolopyridines invoke growing attention,[14,15] their functionalized tetrahydropyrrolo[3,2-*c*]pyridine analogues, including the ensembles with other heterocyclic systems, remain little explored. To meet this synthetic challenge, we disclose here a three step route to substituted 2-(pyrazol-5-yl)-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridines based on readily available 2,2,6,6-tetramethylpiperidin-4-one oxime, acetylene and aroylbromoacetylenes as starting materials.

The first step is the synthesis of 4,4,6,6-tetramethyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridines **1a**,**b** from 2,2,6,6-tetramethylpiperidin-4-one oxime and acetylene in KOH/DMSO system. Compound **1a** was synthesized in 67% yield using the improved known procedure,[14(a)] namely KOH in an amount equimolar to oxime, DMSO, H_2O in 10% volume of DMSO, 80–85 °C for 5 h and acetylene under initial pressure of ~16 atm. The 1-vinyl analogue **1b** was obtained in 79% yield in a similar manner using equimolar amounts of KOH and oxime, DMSO, 85–90 °C for 4 h and ~16 atm acetylene (Scheme 1). Compound **1a** containing NH-pyrrole ring was used further for the synthesis of its *N*-hexyl derivative **1c**.

The second step involves the cross-coupling of pyrrolopyridines **1a–c** with aroylbromoacetylenes **2a**,**b** in a solid K_2CO_3 medium according to the published procedure.[16] Given the presence of an extra NH function in molecules **1a–c**, the chemo- and regioselectivity issues become important here. Apart from the desired ethynylation at the 2-position of pyrrole ring, a nucleophilic addition of both NH functions to the triple bond, or cross-coupling at the 5-position of compounds **1a–c**, or a cleavage of the tetrahydropyridine ring can occur as side reactions.[14(c)] Fortunately, this step proved to be selective, and the products of ethynylation at the 2-position, namely compounds **3a–f**, were the only isolated products (see Scheme 1).

The use of K_2CO_3 appeared to be essential, since it effectively trapped the released HBr and thus prevented the salt formation from the extra NH function of the tetrahydropyridine moiety. Indeed, when Al_2O_3 instead of K_2CO_3 was used as an active medium, the reaction of heterocycle **1c** with benzoylbromoacetylene **2a** afforded hydrobromide salt **5** in 30% yield (Scheme 2). Upon treatment of the aqueous solution of salt **5** with ammonia, compound **3c** was obtained in 61% yield.



Scheme 1 *Reagents and conditions*: i, for **1a**: acetylene, 16 atm, KOH, DMSO, H_2O, 80–85 °C, 5 h; for **1b**: acetylene, 16 atm, KOH, DMSO, 85–90 °C, 4 h; ii, *n*-hexyl bromide, KOH, DMSO, room temperature, 16 h; iii, K_2CO_3, room temperature, 7 h; iv, NH_2NH_2, EtOH, H_2O, 40 °C, 2 h.

At the third step of the sequence, the formation of pyrazole ring from the acetylenic moiety of compounds **3a–f** occurs *via* ring closure with hydrazine in EtOH at 40 °C for 2 h, affording 2-(3-aroylpyrazol-5-yl)-4,4,6,6-tetramethyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridines **4a–e** in 92–98% yields (see Scheme 1). Besides being relevant objects for pharmacology, these products are potential sensors for environmentally unfriendly ions, since, for example, similar pyrrole–pyrazole ensembles were reported to be naked eye no–yes type detection systems for fluoride anion.[17]

In summary, a three step route for the efficient synthesis of 2-(3-aroylpyrazol-5-yl)-4,4,6,6-tetramethyl-4,5,6,7-tetrahydropyrrolo[3,2-*c*]pyridines from readily available 2,2,6,6-tetramethylpiperidin-4-one oxime using acetylene based reactions, has been realized. The obtained compounds contain the pharmaceutically relevant pyrrolopyridine core and represent new tools for potential application in medicinal chemistry and as fluorescence sensors.

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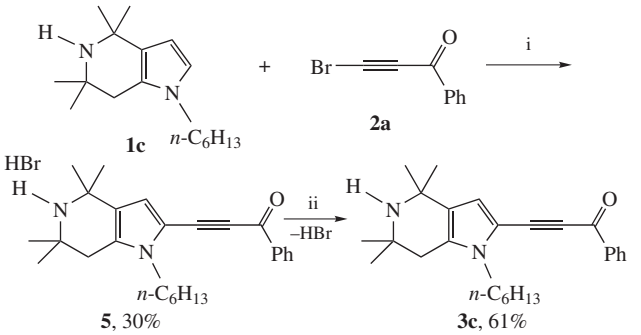

Scheme 2 *Reagents and conditions*: i, Al_2O_3, room temperature, 24 h; ii, aq. NH_3, room temperature.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.018.

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