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Acyl-tetrahydroindolyl-capped 1,3-diynes in oxidative [4+2]-cycloaddition with benzylamine: a one-pot access to 2-acyl-6-phenyl-5-tetrahydroindolylpyridines

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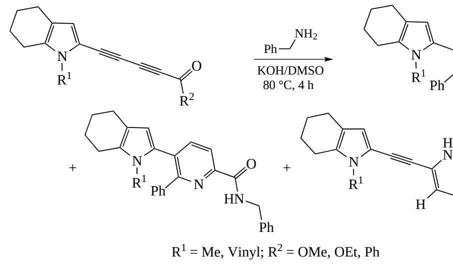
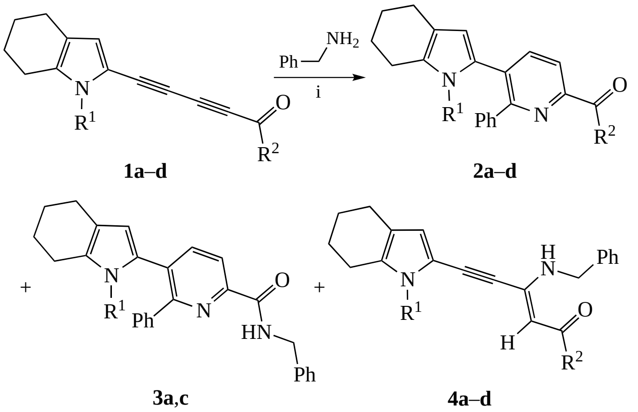
1-Acyl-4-tetrahydroindolyldiynes (available from cross-coupling of 4,5,6,7-tetrahydroindole with 1-acyl-4-bromo-1,3-diynes) undergo oxidative [4+2]-cycloaddition with benzylamine in KOH/DMSO or K_3PO_4/DMSO systems (80 °C, 4 h) to afford 2-acyl-6-phenyl-5-tetrahydroindolyl-pyridines in ~40% yields. Non-catalyzed reaction of the same reactants in boiling MeOH (4 h) or in DABCO/MeCN system (reflux, 1 h) gives 3-benzylaminoalk-2-en-4-ynones in ~40% yields.



R^1 = Me, Vinyl; R^2 = OMe, OEt, Ph

Keywords: tetrahydroindole, tetrahydroindolyldiyne, benzylamine, tetrahydroindolylpyridine, 3-benzylamino-2,4-enyne.

Acyl(alkoxycarbonyl)-tetrahydroindolyl-capped 1,3-diynes of type **1** (Scheme 1), now available *via* the K_2CO_3-promoted cross-coupling of tetrahydroindoles with 1-acyl(alkoxy-carbonyl)-4-bromoalkadiynes,[1] represent promising versatile building blocks for design of tetrahydroindole/diverse heterocycle ensembles due to highly reactive diacetylene four-carbon system capable of various cycloaddition reactions and ability of the tetrahydroindole moiety to be further functionalized with subsequent aromatization to the indole ring. Such compounds open an easy access to novel functionalized indole derivatives with physiologically-oriented valuable properties. In turn, 4,5,6,7-tetrahydroindole and its 1-vinyl derivatives are easily obtained in high yields by the Trofimov reaction[2] from industrial cyclohexanone oxime and acetylene.

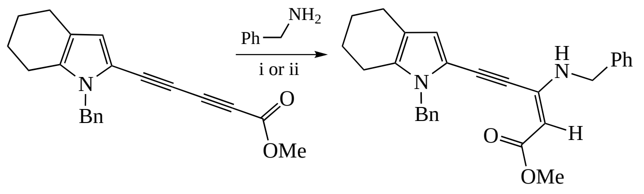


a R^1 = Me, R^2 = OMe **c** R^1 = CH=CH$_2$, R^2 = OEt
b R^1 = Me, R^2 = OEt **d** R^1 = Me, R^2 = Ph

Scheme 1 *Reagents and conditions*: i, KOH or K_3PO_4, DMSO, 80 °C, 4 h. Isolated yields: **2a**, 41%; **2b**, 42%; **2c**, 40%; **2d**, 8% (80% purity); **3a**, (5%); **4a** (10%); **4d** (17%).

Commonly, 1,3-diynes readily add nucleophiles such as primary and secondary amines, amino acids, hydrazines, hydroxylamine, α-imino nitriles, guanidine, H_2O, Na_2S, to form either mono- or diadducts,[3] or various cyclic products.[4–11] The products structure is determined by the nature of substituents in diacetylene, nature of the nucleophile and the reaction conditions, the latter often being a crucial factor. For instance, various 1,4-diaryl-1,3-butadiynes bearing both electron-acceptor and electron-donor substituents undergo (100 °C, 24 h) [4+1]-cycloaddition with anilines in the presense of 10 mol% of CuCl to deliver pyrroles in high yields.[4(a),12] The same substituted diacetylenes add benzylamines (K_2CO_3/DMF, 140 °C, 10 h) to selectively form triarylpyridines.[7(b)] At the same time, in the system KOH/DMSO the above diacetylenes react with primary amines under milder conditions (80 °C, 4 h) to give 1,2,5-trisubstituted pyrroles in high yields.[4(b)] It is worthwhile to underline that in all the aforementioned transformations, 1,4-diarylbutadiynes were mainly employed.

In this consice communication, we report on the preliminary assessment of 1-acyl-4-tetrahydroindolyl-1,3-butadiyne reactivity in the reaction with benzylamine under various conditions. After a series of experiments, we have found that in the KOH/DMSO or K_3PO_4/DMSO systems (80 °C, 4 h), 1-acyl(alkoxycarbonyl)-4-tetrahydroindolyl-1,3-butadiynes **1a–d** with benzylamine gave 2-acyl-6-phenyl-5-(tetrahydro-indolyl)pyridines **2a–d** in ~40% yields, along with pyridines **3**, and (*Z*)-3-benzylamino-4-tetrahydroindolylalk-2-en-4-ynones **4**



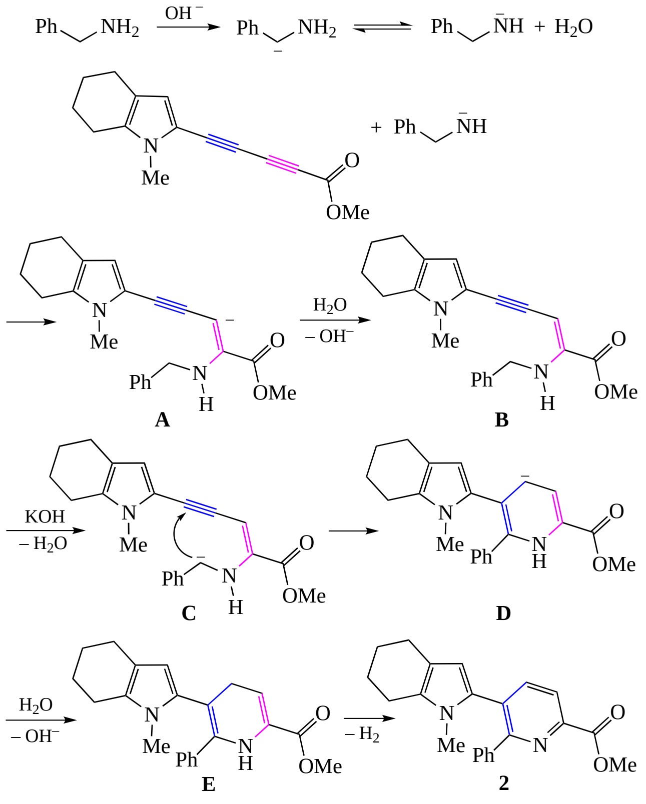
1e **5a**,**b**, 39–40%

Scheme 2 *Reagents and conditions*: i, MeOH, reflux, 12 h; ii, DABCO, MeCN, reflux, 2 h.

(see Scheme 1).[†] Obviously, pyridine carboxamides **3a**,**c** are resulted from the action of benzylamine at the ester group of compounds **2a**,**c**. Surprisingly, as mentioned above, in the case of 1,4-diaryldiynes under these conditions only 1,2,5-triarylpyrroles were formed.[4(*b*)]

Another diyne **1e** at reflux with benzylamine in MeOH without a catalyst delivered *E*-configured 3-benzylamino-5-tetrahydroindolylpent-2-en-4-ynoate **5** (Scheme 2). Notably, in the presence of equimolar amount of DABCO in MeCN this reaction proceeded with almost the same result.

The configuration of the double bonds in compounds **4** and **5** was assigned indirectly by the ^{1}H NMR data using the value for the NH proton shift. In isomer **5**, it is detected at 5.04 ppm (overlapped with the PhCH_2 signals). In isomer **4**, it appears as a downfield triplet at 11.6 ppm, which may be explained by the formation of the intramolecular hydrogen bond NH···O=C.



Scheme 3

Apparently, the building up of the pyridine ring of tetrahydroindolyl pyridines **2** (Scheme 3) starts with the attack of N-deprotonated benzylamine at the C^1 atom of the diyne system. After protonation of carbanion **A**, intermediate **B** thereby formed would undergo the ring closure *via* the attack of benzyl carbanion **C** at C^4 atom of the intermediate. the following quenching of carbanion **D** with trace water of the medium should give dihydropyridine **E** which is oxidized with either DMSO or air oxygen to produce final pyridine **2**.

The deprotonation of the CH$_2$ group in intermediate **B** is likely facilitated by the neigbouring electron-acceptor acyl group. The first step of the reaction (the attack of N-centered anion at the C^1 position) is probably charge controlled since the C^1 position has a larger positive charge relative to other carbon atoms of the diyne system that roughly follows from ^{13}C NMR shifts: C(1) (83.45), C(2) (79.76), C(3) (80.22), C(4) (81.79) ppm. If to assume that the benzylamine carbanion can attack the position 4 of the diyne chain, the formed pyridine should possess a different substitution pattern, *viz*., the pyrrole substituent should be located at position 6 of the pyridine ring.

The reaction delay on the formation of enyne **5** in the non-catalytic reaction in methanol may be expalined by a larger distance between the benzyl methylene group and electron-acceptor functions. The different configuration of the adducts **4** and **5** obtained in KOH (K$_3$PO$_4$)/DMSO (*Z*-isomer), on the one hand, and in methanol at reflux or in DABCO/MeCN (*E*-isomer), on the other hand, indicates the different mechanism of their formation. The first is the classic nucleophilic addition to the electron-deficient triple bond, which procceds as *trans*-attack to give the *Z*-adducts. The second one likely represents the *cis*-addition of non-ionized benzylamine to the acetylenic moiety where the emerging negative charge is simultaneously stabilized at C^1 position by the NH-proton that provides *E*-configuration. This is one of the possible explanations for the difference in the configuration of adducts **4** and **5**. The influence of the substituent at the nitrogen atom on this process is also not excluded.

In summary, the one-pot synthesis of 2-acyl-6-phenyl-5-tetrahydroindolylpyridines from 1-acyl-4-tetrahydroindolyl-1,3-butadiynes and benzylamine here developed can be considered as a first example of a possible general approach to design indole-ring heterocyclic structures by exploiting the ability of 1,3-diyne systems to be a platform for diverse biologically potent heterocycles (pyrroles, pyrazoles, isoxazoles, pyridines, pyrimidines, furans, thiophenes). This is warranted by the accessibility of tetrahydroindole acyl-caped 1,3-diynes *via* the K$_2$CO$_3$-promoted cross-coupling of tetrahydroindoles with acylbromodiynes.

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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.2022.11.007.

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[†] *Reaction of pyrrolyldiynes with benzylamine.* A mixture of pyrrolyldiyne **1a**–**d** (1.00 mmol), KOH·0.5H$_2$O (20 mg, 0.30 mmol) and benzylamine (161 mg, 1.50 mmol) in DMSO (2.5 ml) was heated at 80 °C for 4 h. After cooling, the mixture was diluted with brine (3 ml), extracted with diethyl ether (5×3–5 ml). The ether extracts were washed with water (5×5 ml) and dried over K$_2$CO$_3$. The residue after removing the solvent was fractionated by column (SiO$_2$, *n*-hexane, *n*-hexane–diethyl ether, 9:1, 5:1) and preparative thin-layer (SiO$_2$, *n*-hexane–diethyl ether, 1:1) chromatography to give compounds **2a**–**d**, **3a**, **4a**,**d**. Compounds **3c**, **4b**,**c** formed in trace amounts were detected by ^{1}H NMR.

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