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Note

Pauson–Khand reaction of 2-ethynyl aniline: Synthesis of fused ring indoles by organocuprate conjugate addition followed by spontaneous dehydration

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Abstract

The Pauson–Khand reaction of 2-ethynyl aniline gives the expected cyclopentenone product, with the aniline alpha to the ketone. Treatment with organocuprates gives not the simple conjugate addition product, but the indole derived from an addition–cyclisation–nucleophilic attack sequence.

Keywords: Pauson Khand; Cuprate; Indole

1. Introduction

The Pauson–Khand (PK) reaction [1], the $Co_2(CO)_8$-mediated cyclisation of an alkyne and alkene and CO, is of interest due to easy carbon–carbon bond formation, often with high regio- and stereo-control. Many variations have been developed including the use of catalytic cobalt, [1b] other cobalt sources, [1c] other metals, [1d] heterometallic clusters [1e] and asymmetric variations based on either chiral ligands on metals [1f] or chiral auxiliaries on the substrates [1g]. This group has been interested in the PK reactions of alkynes bearing unusual structural features [1h] and in other reactions of cobalt carbonyls [1i] with unsaturated species, and was interested to investigate the PK reactions of alkynes bearing other groups which may potentially coordinate to cobalt and thus influence the stereo- or regio-chemistry of the PK. For instance, it has been demonstrated that certain alkynyl thiols are effective chiral auxiliaries in the PK [1g] as the sulphur acts as a hemilabile donor influencing the diastereoselectivity of the reaction. 2-Alkynyl anilines seemed interesting substrates for the PK as if the reaction were to proceed in the expected manner the products would contain an aniline nitrogen which would seem well positioned for condensation with the cyclopentenone carbonyl to give products which could tautomerise to alkenyl indoles (Scheme 1).

There appears to be only one reference to the PK reactions of alkynyl anilines [2]. In these systems the nitrogens were protected, which could explain the lack of both unusual reactivity and product self-condensation. However, there has recently [3] been a report of some unexpected and unusual products derived from the dicobalthexacarbonyl complexes of alkynyl anilines, and so it was difficult to predict the reactivity of such species.

2-Ethynyl aniline [4] **1** reacted smoothly with dicobaltoctacarbonyl to give the dicobalt hexacarbonyl adduct, with no evidence from IR or NMR (^{1}H and ^{13}C) of the aniline nitrogen acting as a donor. This complex upon treatment with norbornadiene (4 mol. equvi.) in DCM at reflux for 3 h gave the expected PK product **2** as a single regio- and diastereo-isomer in 67% yield after

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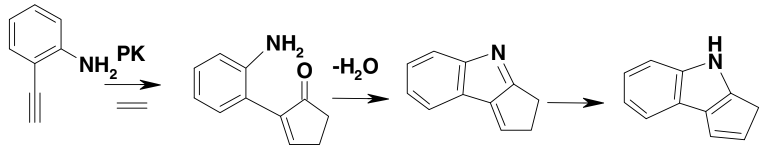


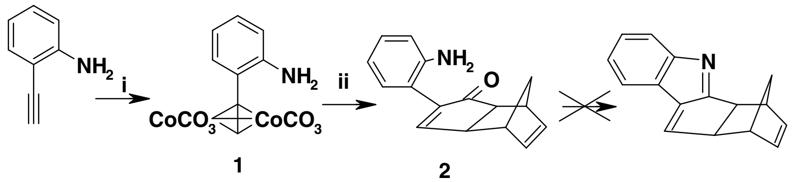
Scheme 1.

work-up and crystallisation from ethanol–water. The anticipated condensation, however, proved elusive and no evidence of condensation was observed under a variety of conditions (neutral, acids, CSA, TsOH, reflux in EtOH, PhMe, Dean and Stark) only decomposition to an intractable material believed to be polymeric due to low solubility and very broad NM resonances. It seemed likely that the α–β unsaturated ketone was either not sufficiently electrophilic to react with the aniline, or that the unsaturated system was simply too strained for the required angle of attack at the carbonyl to be achieved (Scheme 2).

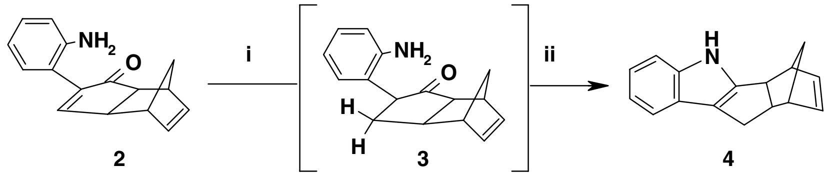
Removal of the alpha–beta unsaturation of the ketone was expected to release the putative reactants from limiting ring strain and simultaneously increase the electrophilicity of the carbonyl carbon, and so the selective conjugate reduction of the α–β unsaturated ketone with Stryker's reagent (hydrido (triphenylphosphine) copper(I) hexamer $[PPh_3CuH]_6$) was examined. After some initial failures with commercial preparations of Stryker's reagent, a recent synthesis of Stryker's reagent [5] using silane reducing agents was followed. The freshly prepared material was used to reduce the PK product **2**, and the indole **4** derived from spontaneous condensation was isolated after column chromatography in 68% yield as a white crystalline solid (Scheme 3).

The indole portion of the molecule gave characteristic signals in the proton and carbon NMR and the totality gave a molecular ion at *M*/*Z* 221 (confirmed by HRMS), leaving no doubt as to the structure of the product.

In order to probe the generality of this combined PK-conjugate addition route to fused bicyclic indoles a small range of other soft nucleophiles were added to the cyclopentenone alkene. Gilman-type cuprates prepared by the addition of methyl, butyl and phenyl lithium to copper iodide successfully gave the corresponding indoles **6a**–**c** in essentially quantitative yield. These compounds were isolated as single diastereoisomers, of high purity, which could be further purified by recrystallisation from the reaction mixture without chromatography (Scheme 4). In no cases was the uncyclised product **5** observed, and examination of the crude reaction mixtures by NMR showed no trace of signals which could be assigned to the minor diastereoisomers. The stereochemistry of the indoles **6a**–**c** was initially assigned as illustrated (Scheme 4) from the vicinal coupling of the proton at the new chiral centre. Although many of the resonances are unassignable multiplets, as is common in such systems due to the large number of small couplings broadening many peaks, and the new chiral centre itself is complicated by coupling to the cuprate-derived chain, the proton at the ring fusion adjacent to the site of addition (H10a) has one ca. 7 Hz coupling (in **6a** and **6b**) to it is mutually *cis*-axial neigbor (H4a) and only shows a small (ca. 2 Hz) coupling to any other protons, thus indicating an approximate 90° relationship to the proton at the new chiral centre, consistent with endo-attack. This stereochemistry is easily explicable by considering the overall cup-shaped conformation of **2** (exaggerated for illustrative purposes in Scheme 4)



Scheme 2. (i) Co_2CO_8, (1.1 equvi.). (ii) Norbornadiene 5 equvi. DCM (4 ml/mol) 40 °C, 3 h 67%.



Scheme 3. (i) $[Ph_3PCuH]_6$ 3 equvi. PhMe (25 ml/mmol)/H_2O (5 equvi.) RT 24 h. (ii) Spontaneous. 68% overall.