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Nicholas Reactions of Amines

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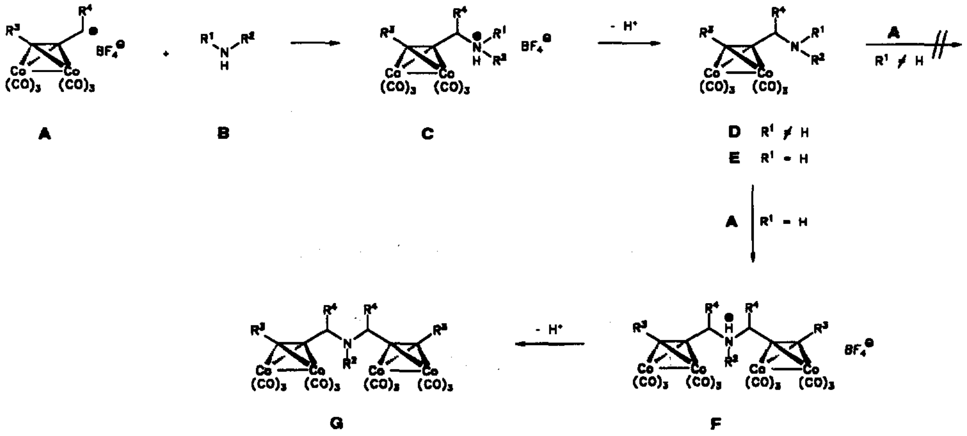
Abstract: An efficient synthesis of mono- and bispropargylated tertiary amines is described, using the Nicholas reaction with primary and secondary amines as nucleophiles.

Since the first paper on this topic appeared in 1977[1], the reaction of dicobalthexacarbonyl stabilized propargyl cations with nucleophiles, now known as the Nicholas reaction, has attracted considerable interest from synthetic organic chemists. The reactions with carbon nucleophiles have been explored to a great extent[2][3], but also oxygen centered nucleophiles were used frequently[4]. However, only little is known about Nicholas reactions with nitrogen nucleophiles. The earliest example, an unoptimized reaction of $[(HC\equiv CCH_2)Co_2(CO)_6]^+BF_4^-$ with CH_3CN in the presence of sulfuric acid dates from 1981[5]. In 1990 french authors described the reactions of the same cobalt complex with pyridine[6] and with one secondary amine[7]. In the same year a Japanese group reported the (in this case undesired) N-propargylation of indole[8] and meanwhile in a recent paper the Nicholas reaction with allylic amides was described[9].

Surprisingly, until now no work has been done concerning a synthetic application of the reaction of amines with cobalt complexed propargyl cations. Therefore we decided to examine this reaction in a general manner and to develop a synthetically useful procedure for the propargylation of primary and secondary amines.

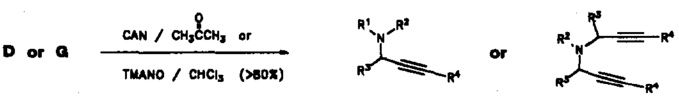
Nucleophilic addition of an amine **B** to a dicobalthexacarbonyl stabilized propargyl cation **A** should lead to the formation of a metal complexed propargylic ammoniumion **C** (SCHEME 1). In the case of a secondary amine ($R^1 \neq H$) deprotonation of this intermediate would give a tertiary amine **D**, which can be expected to show only very little reactivity towards the cation **A**. With primary amines ($R^1 = H$), on the contrary the product of the addition/deprotonation sequence would be a secondary amine **E**, which could undergo the same reaction a second time, yielding a bispropargylated tertiary amine **G**.



SCHEME 1

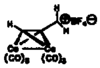
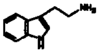
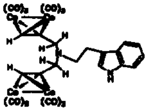
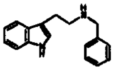
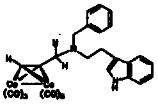
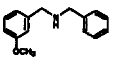
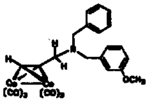
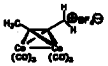
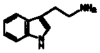
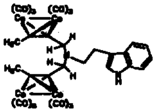
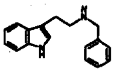
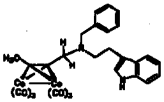
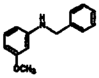
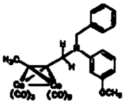
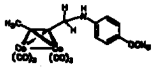
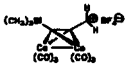
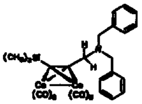
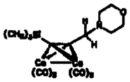
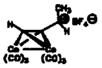
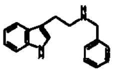
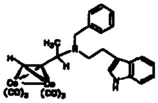
When using secondary amines **B** (R^1 ≠ H) as nucleophiles, the necessary deprotonation could be carried out by a second equivalent of the amine. This is only reasonable for simple, easily accessible compounds. In the case of primary amines (R^1 = H), on the other hand, excess amine would lead to a mixture of mono- and bispropargylated products, which is in fact already observed using equivalent amounts of **A** and **B**[8]. These problems can be circumvented by using an additional base for the deprotonation of **C**. We found N-ethyldiisopropylamine (Hünigs base) most suitable for this purpose. This bulky base combines sufficient basicity against the ammoniumion **C** with poor nucleophilicity towards the cation **A**. Therefore, the reactions are conveniently run in the presence of one or two eqivalents of Hünigs base. A typical experimental procedure is given below[10].

As can be seen from the entries in Table 1, this type of Nicholas reaction can be carried out with primary aliphatic or aromatic amines and with secondary aliphatic or aliphatic-aromatic amines. Thus metal complexed mono- or bispropargylated tertiary amines are formed in generally good yields[11]. The cobalt complexed amines can be efficiently demetalated with Cer-(III)-ammoniumnitrate (CAN) in acetone[12] or with trimethylamine-N-oxide (TMANO) in CHCl$_3$[13] (SCHEME 2), producing the metal free amines in yields generally exceeding 80%.



SCHEME 2

TABLE 1: NICHOLAS REACTIONS WITH PRIMARY AND SECONDARY AMINES

entry	cobalt complexed propargyl cation	amine	product	yield [a]
1				66 %
2				69 %
3				76 %
4				61 %
5				77 %
6				76 %
7				79 %
8				78 %
9				74 %
10				69 %

[a] isolated yields after chromatography

all new compounds were characterized by ^1H and ^{13}C NMR spectroscopy, MS and gave satisfactory elemental analyses

In summary, a simple and efficient procedure for the propargylation of primary and secondary amines by means of dicobalthexacarbonyl stabilized propargyl cations was developed, producing the desired tertiary amines in good overall yields.

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[10] To a magnetically stirred slurry of 4 mmol Co-propargylium salt **A** in 30 mL of dimethoxyethane (DME), cooled to -20°C, is added a solution of 4 mmol of sec. amine (or 2 mmol of prim. amine) and 4 mmol of $EtN(iPr)_2$ in 20 mL of DME. The reaction mixture is stirred for 2 h at -20°C. 50 mL of hexane are added and the precipitated ammonium salt is filtered off. The solvents are removed in vacuo and the oily residue is purified by column chromatography on silica gel with hexanes/ether as eluent.

[11] NMR Data for representative cobalt complexed propargylic amines: entry **1**, ^1H NMR ($CDCl_3$, TMS):δ 3.00 (t, J=7.7 Hz, 2H), 3.12 (t, J=7.7 Hz, 2H), 4.85 (s, 4H), 6.10 (s, 2H), 7.01-7.60 (m, 5H), 7.96 (br s, 1H); ^{13}C NMR ($CDCl_3$, TMS):δ 24.0, 54.3, 56.7, 73.4, 90.1, 111.2, 113.8, 118.6, 119.4, 121.4, 122.1, 127.4, 136.3, 199.8 . entry **3**, ^1H NMR ($CDCl_3$, TMS):δ 3.73 (s, 2H), 3.75 (s, 2H), 3.79 (s, 3H), 3.91 (s, 2H), 6.09 (s, 1H), 6.80-7.36 (m, 9H); ^{13}C NMR ($CDCl_3$, TMS):δ 55.1, 56.7, 58.2, 58.3, 73.4, 90.9, 112.7, 114.1, 121.1, 127.2, 128.3, 128.8, 129.3, 138.6, 140.4, 159.8, 199.8 .

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