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ALLENES AND ACETYLENES XVII.[1] ALLENIC AMINES FROM ORGANOCUPRATE REACTIONS

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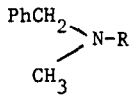
Mitochondrial monoamine oxidase (MAO) is a flavin-linked enzyme which is responsible for the oxidative inactivation of the transmitter amines.[2] Its physiological activity can be modulated by a great number of inhibitors[3] whose actions are exploited clinically, mainly in the treatment of depression.[2a] Among these propargylic amines are the most studied active-site directed, irreversible inhibitors. Their mode of action involves an enzyme-mediated formation of a reactive intermediate of unknown structure which reacts with the flavin component.[4] The structure of the adduct with N,N-dimethyl-2-propynylamine was recently identified as a flavocyanine by Abeles and co-workers.[5] An allenic amine (1a), a known irreversible inhibitor of MAO,[6] was recently shown by Krantz to give an unidentified product with MAO. As shown by UV-visible spectroscopy this adduct is structurally quite different from those obtained with acetylenic amines.[7]

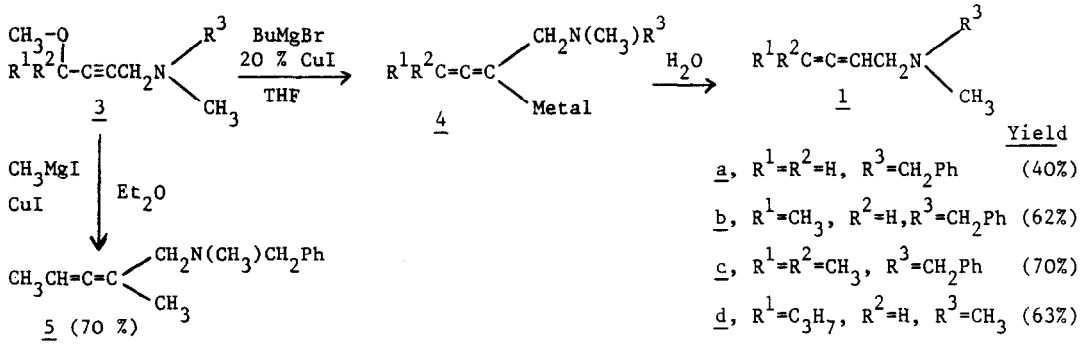


1a R = $CH_2CH{=}C{=}CH_2$

2 R = $CH_2C{\equiv}CCH_3$

In joint efforts Krantz and we are trying to elucidate the structure of the adduct with the allenic amine 1a. For this purpose and for the determination of isotope effects in the enzyme inactivation a method to prepare the amine 1a isotopically labeled in the allenic side chain was needed. The seemingly most direct route via 2,3-butadienol[8] was not judged efficient enough and we therefore developed a novel synthetic method for α-allenic amines.[9] The methods decribed here were also applied to the preparation of allenic amines which will be used in studies of structure-activity relationships.

In certain allene-forming reactions of propargylic compounds with organo cuprates the introduction of hydrogen instead of an alkyl group has been noted.[10,11,12] We here report that acetylenic amino ethers of the general type 3 upon treatment with butylmagnesium bromide and copper(I)iodide (5+1 equiv.) in tetrahydrofuran (THF) or THF-ether (~ 3:1) give rise to an organometallic intermediate (4) which can be hydrolysed to an allenic amine (1).[13]



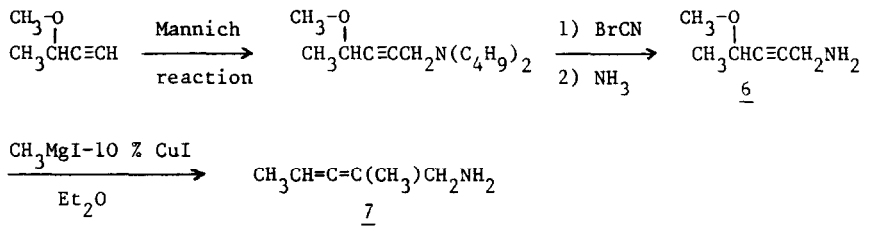
	Yield
a, $R^1=R^2=H$, $R^3=CH_2Ph$	(40%)
b, $R^1=CH_3$, $R^2=H$, $R^3=CH_2Ph$	(62%)
c, $R^1=R^2=CH_3$, $R^3=CH_2Ph$	(70%)
d, $R^1=C_3H_7$, $R^2=H$, $R^3=CH_3$	(63%)

The reaction conditions comprise the following steps: (i) addition of CuI to the Grignard reagent under nitrogen at -20 °C and stirring for 10 min (ii) addition of the acetylene 3 and allowing the mixture to reach room temperature (iii) stirring until the reaction is complete or > 90 % (3-6 h) and hydrolysis at 0 °C. The yields of the distilled amines 1a-d varied between 40-70 %.[14] The low yield of 1a (isolated in mixture with 2) is caused by the simultaneous formation in the protonation step of an equal amount of the acetylene 2. For the other amines (R^1 and/or R^2 = alkyl) the protonation is highly regioselective giving rise to only trace amounts of the isomeric acetylenes. The latter are easily removed by recrystallisation of the oxalates or hydrochlorides of the allenic amines.

Surprisingly, a tert-butyl-containing amino ether 3 (R^1 = tert-butyl, R^2 = H, R^3 = CH_2Ph) repeatedly failed to react under the above reaction conditions.[15]

The choice of THF or THF-ether (~3:1) is crucial in steering the reaction of 3 in the desired direction. Ether as the solvent gives mainly alkylated alleneamines e.g. 5 which was formed in 95 % yield (GLC) when the corresponding amino ether reacted with methylmagnesium iodide in the presence of CuI (5+1 equiv.) at room temperature overnight.[16]

Preliminary attempts to reduce primary or secondary amines corresponding to 3 under the above conditions led to mixtures of products. However, the reaction of the primary amine 6[17] with a fivefold excess of CH_3MgI-CuI in ether gave the alkylated allene 7 in moderate yield (~75 %, GLC). It is essential first to add the acetylene 6 to the Grignard reagent and then CuI (cf. ref. 10a).



Since the amino ethers 3 are prepared through the Mannich reaction isotopic labels can be conveniently introduced via paraformaldehyde. Although the desired amine 1a is only formed in about 40 % yield the method is still useful on a small scale because compound 3 is formed in a high yield and purification before the final step can be omitted. The preparation and use of the labeled compounds will be reported elsewhere as will the structure-activity

studies.[18]

NMR data of the allenic amines ($CDCl_3$, δ)

1a	7.3 (m, 5H), 5.4-4.9 (m, 1H), 4.8-4.6 (m, 2H), 3.50 (s, 2H), 3.2-3.0 (m, 2H), 2.20 (s, 2H)
1b	7.3 (m, 5H), 5.3-5.0 (m, 2H), 3.53 (s, 2H), 3.3-3.0 (m, 2H), 2.25 (s, 3H) 1.8-1.6 (m, 3H)
1c	7.3 (m, 5H), 5.2-4.8 (m, 1H), 3.52 (s, 2H), 3.00 (d, 2H), 2.22 (s, 3H), 1.67 (d, 6H)
1d	5.3-5.0 (m, 2H), 3.1-2.8 (m, 2H), 2.30 (s, 6H), 2.2-1.3 (m, 4H) 1.00 (t, 3H)
5	7.3 (m, 5H), 5.2-4.8 (m, 1H), 3.51 (s, 2H), 2.91 (d, 2H) 2.20 (s, 3H), 1.75 (d, 3H) 1.67 (d, 3H)
7	5.4-5.1 (m, 1H), 3.12 (d, 2H), 1.81 (d, 3H), 1.75 (d, 2H), 1.52 (s, 2H)

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13. In contrast to Crabbé and co-workers (ref. 11) and the Utrecht group (ref. 12) we do not postulate formation of the allenes from hydrolysis of a Cu(III)-intermediate; the reaction temperature and the fact that 0.25 equiv. of CuI gives the same result precludes such an intermediate as the immediate precursor of the alleneamines. The presence of 4 was indicated through hydrolysis with D_2O.
14. Compounds were identified by IR, NMR and mass spectrometry and in most cases by elemental analysis of their oxalates.
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