A New β-Arylethylamine Synthesis by Aryl Aldehyde Homologation

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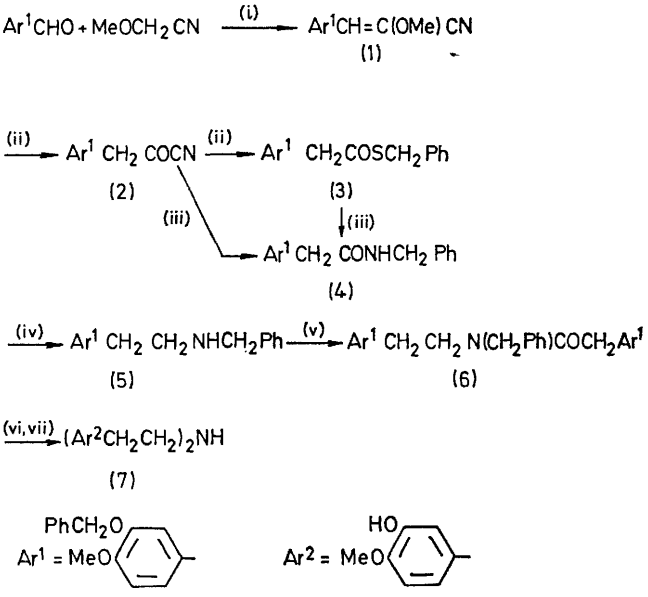
Summary β-Arylethylamines can be generated in good yield by condensation of an aryl aldehyde with methoxyacetonitrile followed by demethylation of the α-methylcinnamonitrile product with sodium benzylthiolate in the presence of an amine and subsequent reduction with lithium aluminium hydride.

As part of our work on alkaloid biogenesis, we required a versatile and efficient method for the generation of mono- and di-β-arylethylamines from the available vanillin/isovanillin units. We now report a process which offers advantages over the commonly used cyanide[1,2] and nitrostyrene[3] routes. The method is exemplified by the synthesis of the compound (**6**) (Scheme).

O-Benzylisovanillin was treated with an equivalent of the sodium salt of methoxyacetonitrile in excess of methoxyacetonitrile and dimethylformamide (N_2) at 110° to give α-methoxycinnamonitrile† (**1**), m.p. 85—87° (81%). The enol ether function was demethylated with sodium benzylthiolate (1 equiv.) in dimethylformamide under N_2 at 110°, during 5 min, benzylamine being added concurrently with the thiol. The presumed thiol ester intermediate (**3**) [derived from the aroyl cyanide (**2**)] and/or the cyanide (**2**) were captured by the added benzylamine (1 equiv.) to give the benzylamide (**4**) (95%). This was reduced to the amine (75%) with lithium aluminium hydride in tetrahydrofuran under reflux. This secondary amine was then utilized as the nucleophilic component in a second acylation step (as above) to form the tertiary amide (**6**) (80%). Reduction and debenzylation of this as previously described[4] gave the diphenethylamine (**7**). The overall yield from *O*-benzylisovanillin was 27%.

In contrast to previous syntheses, the two aralkyl units are derived from a common intermediate with a consequent diminution in the number of steps involved. The yields are comparable.[4]



SCHEME. (i) NaH–DMF; (ii) BzS^-Na^+; (iii) $PhCH_2NH_2$; (iv) $LiAlH_4$; (v) (**1**) + BzS^- Na^+; (vi) $LiAlH_4$; (vii) H_2/Pd/C.

In addition, as will be exemplified later, this route permits the efficient synthesis of 1-benzyl-1,2,3,4-tetrahydroisoquinolines. The use of the anions of cyanohydrin ethers in synthesis has recent precedent.[5]

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† All new compounds gave correct microanalysis and the expected spectral data.

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