NOVEL SYNTHETIC METHOD OF TOBACCO ALKALOIDS : FORMATION OF N,α-DILITHIATED N-PYRIDYLMETHYLBENZAMIDES AND THE REACTION WITH DIELECTROPHILES

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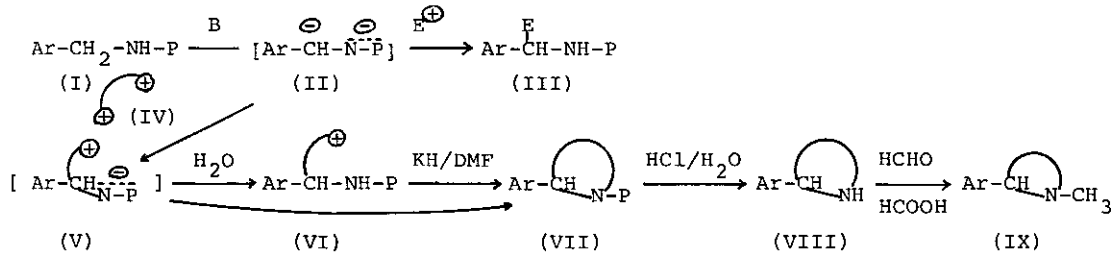
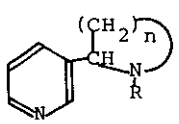
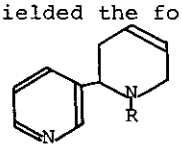
We have investigated the formation of N,α-dianion(II) bearing a heteroaromatic ring(Ar: furan, thiophen, pyridine) and the reaction with various electrophiles($E^{\oplus}$) to give α-alkylated amine derivatives(III). This method was applied to the synthesis of Tobacco alkaloids bearing a pyridine ring.



3-Aminomethylpyridine derivative(I), N-protected with benzoyl group, underwent efficient and regioselective lithiation on treatment with LDA/THF(-70%~-85°C) to give N,α-dilithium salts(II), which reacted with α,ω-dielectrophiles(IV) such as $Br-(CH_2)_n-X$ or $Cl-CH_2CH=CHCH_2-Cl$(cis) to yield N-(3-pyridyl-α-halogenoalkylmethyl)benzamides(VI). The cyclization of (VI) to azacycloalkanes(VII) via intramolecular C-N bond formation was achieved with KH/DMF(-10 ~-15°C). (VII) could also be obtained by one-pot reaction from (II) without isolation of (VI). Hydrolysis of N-benzoyl derivatives(VII) with 6N-HCl followed by methylation with HCHO/HCOOH yielded the following Tobacco alkaloid:



1. n=3,R=H(dl-nornicotine)
2. n=4,R=H(dl-anabasine)
3. n=3,R=Me(dl-nicotine)
4. n=4,R=Me(dl-N-Me-anabasine)



5. R=H(dl-anatabine)
6. R=Me (dl-N-Me-anatabine)

Similar procedure was applied not only to the synthesis of 2- and 4-pyridyl derivatives but also to the formation of other derivatives with 4- and 7-membered azacycloalkanes(n=2,5).