Activated Imines as Carbon Electrophiles: Applications in Alkaloid Synthesis

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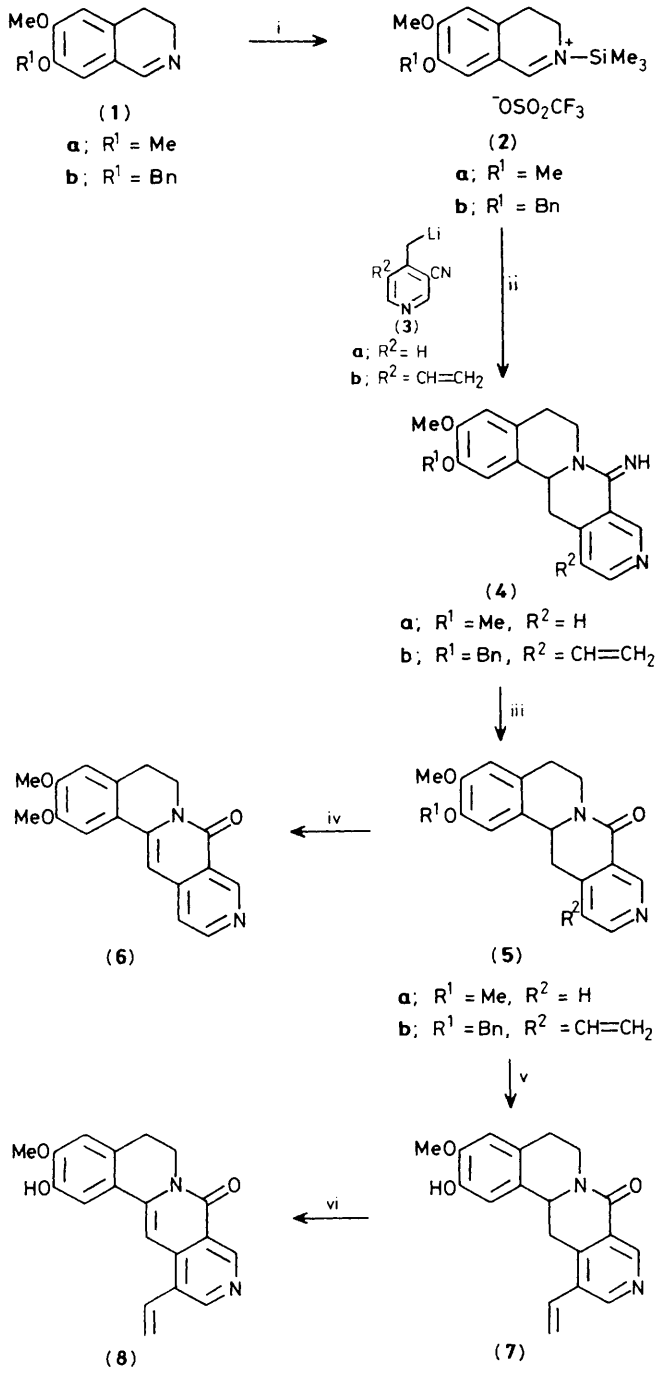
3,4-Dihydroisoquinolines and 3,4-dihydro-β-carbolines react with trimethylsilyl trifluoromethanesulphonate to form complexes that react readily with the lithio derivatives of 3-cyano-4-methylpyridines; the method has been applied to the synthesis of the *Alangium* alkaloids, (±)-alangimaridine and alangimarine.

The reaction of carbanion equivalents with imines is generally a useful procedure for the formation of carbon–carbon bonds α to a nitrogen atom.[1] When the reaction with neutral imines fails to occur, the more electrophilic iminium salts may often be used in their stead. Addition of a nucleophile to an imine yields initially an amide anion that may accept a proton to form a secondary amine or, alternatively, may react intramolecularly with a suitably disposed electrophilic centre.[1,2] Iminium salts, although more reactive, are not as versatile reagents because the products of addition are tertiary amines with a more limited scope than secondary amines for further reaction at the nitrogen atom. A reagent that would activate the imine by quaternization and that would subsequently be readily removable would therefore be highly desirable in synthesis. We have found that trimethylsilyl trifluoromethanesulphonate (triflate) fulfils this purpose and report here its use in the synthesis of several isoquino[2,1-*b*][2,7]naphthyridines, including the alkaloids alangimaridine (**7**) and alangimarine (**8**), and several indolo[2′,3′;3,4]pyrido[1,2-*b*][2,7]naphthyridines.

Trimethylsilyl triflate has been used previously in the presence of triethylamine to convert imines into enamines[3,4] but to our knowledge its use to activate an imine towards nucleophilic attack has not been reported.

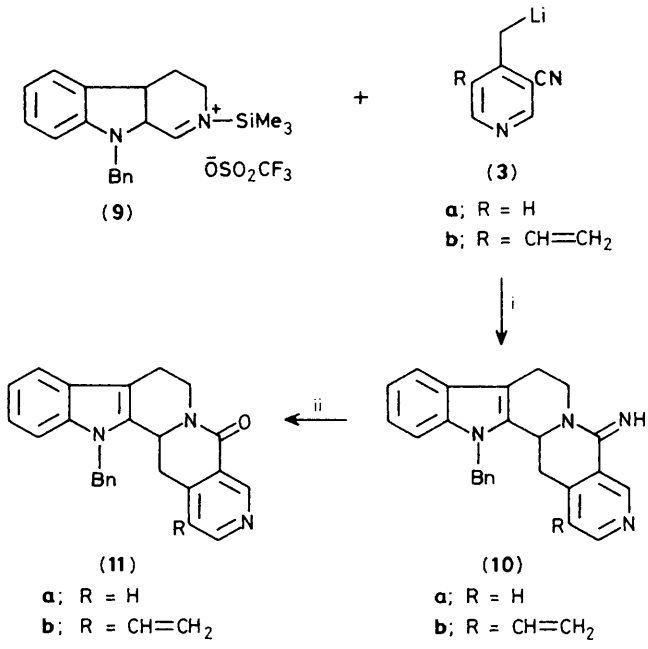
In a model study we found that (**1a**) reacted with trimethylsilyl triflate forming a complex, formulated as (**2a**) (Scheme 1), and that the latter upon treatment with the lithio derivative of 3-cyano-4-methylpyridine (**3a**) (derived from 3-cyano-4-methylpyridine[5] by treatment with lithium di-isopropylamide) afforded the amidine (**4a**). The mode of cyclization is probably similar to that described for the reaction between (**1a**) and lithiophthalide reagents.[2] The exact role of the trimethylsilyl group in this reaction has not been clarified, but the reactions reported here did not proceed in the absence of this reagent. It seems likely however that it resides eventually on the amidine nitrogen atom and is lost on work-up. Hydrolysis of (**4a**) yielded the lactam (**5a**), an analogue of the alkaloid alangimaridine, which upon oxidation with iodine in methanol afforded (**6**), an analogue of alangimarine. Compound (**6**) has been prepared previously.[6–8]

The synthesis of the alkaloids was accomplished using a different set of starting materials, namely (**1b**) and (**3b**).[9] Compounds (**4b**) and (**5b**) were formed in excellent yields and the latter was converted into (±)-alangimaridine (**7**) by debenzylation. Dehydrogenation of (**7**) with iodine in methanol afforded alangimarine (**8**). The spectroscopic properties in solution of (**7**) and (**8**) agree with those reported for the natural alkaloids.[10] Alangimarine (**8**) has been previously synthesized through photochemical cyclization of the appropriate enamide.[11]



Scheme 1. *Reagents and conditions:* i, $Me_3SiOSO_2CF_3$, tetrahydrofuran (THF), 0 °C, 2 h; ii, THF, −40 °C, 3 h; 20 °C, 12 h: (**4a**), m.p. 160—163 °C, 97%; (**4b**), m.p. 218—222 °C, 83%; iii, 20% KOH, reflux, 48 h: (**5a**), m.p. 173—175 °C, 97.5%; (**5b**), m.p. 175—177 °C, 98%; iv, I_2, MeOH, reflux, 8 h: (**6**), m.p. 185—186 °C, 94%; v, conc. HCl, reflux, 1 h; (**7**), m.p. 242—245 °C, 97%; vi, I_2, MeOH, reflux, 8 h; (**8**), m.p. 235—237 °C, 86%.

The usefulness of trimethylsilyl triflate as a removable activating group in imine chemistry has been further demonstrated in the reactions between (**9**) and (**3a**) and (**3b**) (Scheme 2). The amidines (**10a**) and (**10b**) were formed in high yield and converted by hydrolysis into the lactams (**11a**) and (**11b**), respectively. Compounds (**11a**) and (**11b**) are *N*-benzyl



Scheme 2. *Reagents and conditions:* i, THF, −40 °C, 3 h: (**10a**), m.p. 190—192 °C, 89%; (**10b**), m.p. 276—278 °C, 86%; ii, 20% KOH, reflux, 48 h: (**11a**), m.p. 125—127 °C, 89%; (**11b**), m.p. 226—230 °C, 94%.

derivatives of 3,14-dihydronaucléfine[12] and 3,14-dihydroangustine,[13] respectively.

All of the compounds were homogeneous on t.l.c. in several solvent systems and the spectral data (^1H and ^{13}C n.m.r.; mass) were consistent with the assigned structures.

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