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ISOQUINOLINE FRAMEWORKS VIA ARYL RADICAL-INITIATED 1,6-CYCLIZATION

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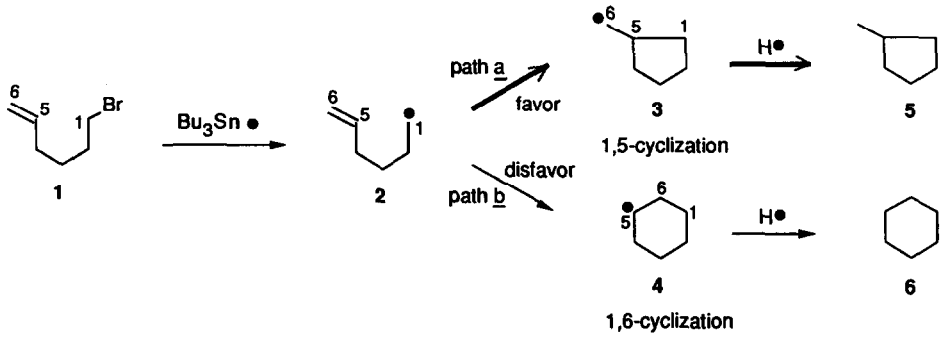
Summary: Exclusive1,6-cyclization occurred to afford isoquinoline frameworks when the enamide and the enamine substrates bearing *exo*-olefin moiety were treated with tri-*n*-butyltin hydride in the presence of radical initiator (**9a, b** → **12a, b**; **13a, b** → **18a, b**), respectively. On the other hand, competitive 1,6- and 1,5-cyclization occurred to give a mixture of isoquinolone and isoindolone frameworks when the enamide substrates bearing *endo*-olefin moiety were treated under the same conditions (**22a, b** → **26a, b** and **27a, b**).

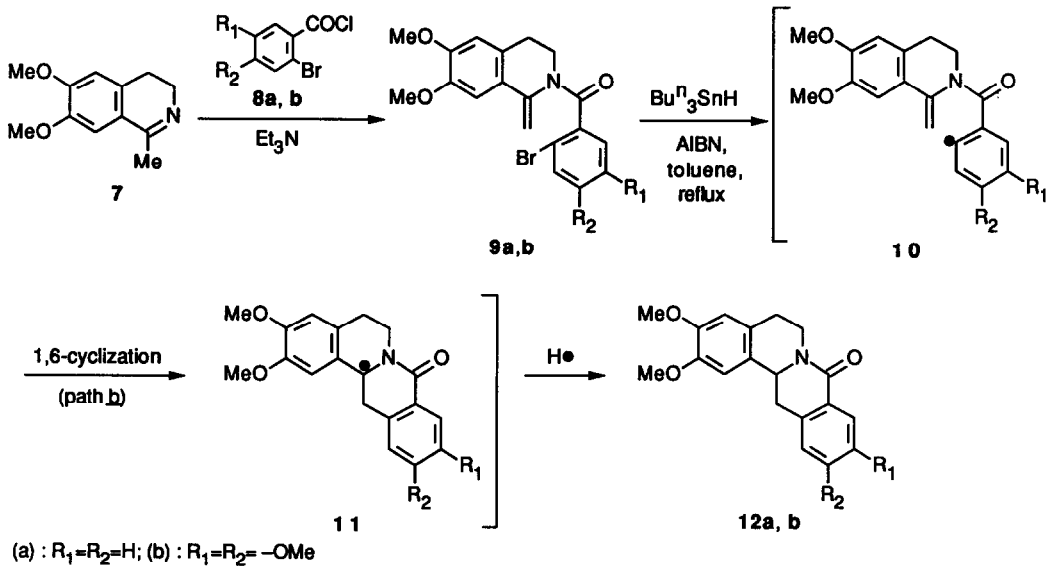
It has been reported that 5-hexenyl radical cyclized predominantly to the smaller five membered ring than the larger six membered ring owing to take stereoelectronically more favorable transition state in the former 1,5-*exo*-cyclization (path a) though it results unstable primary radical intermediate[1] (Scheme 1). Since we are interested in the particular case where highly stabilized radical intermediate could be expected in the competing 1,6-*endo*-cyclization (path b), three groups of the enamide and the enamine substrates conjugated to aromatic ring were prepared and subjected to the radical reaction conditions.[2]



Scheme 1

The substrates belong to the first group were the bromo-enamides, **9a** and **9b**, which were prepared in satisfactory yields by treating the known 1-methyl-3,4-dihydroisoquinoline[3] (**7**) with the corresponding acid chloride (**8a** and **b**) in the presence of triethylamine, respectively. This type of the enamides have so far been used as the substrates for the construction of the protoberberine framework in both the photochemical 1,6-electrocyclization[4] and the Heck type palladium mediated 1,6-cyclization.[5] When **9a** was treated with tri-*n*-butyltin hydride (2 equiv.) in boiling toluene in the presence of a catalytic amount of AIBN exclusive 1,6-cyclization (path b) occurred to give the six-membered lactam (**12a**) in 60.5% yield as a single cyclization product presumably via the highly

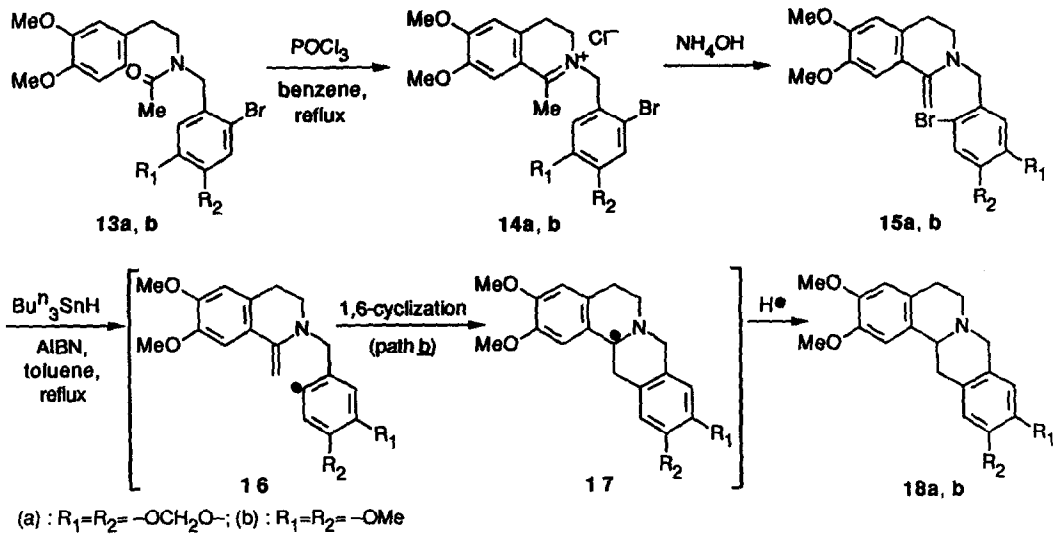
stable benzylic radical intermediate (**11**). On the same treatment, **9b** afforded the 1,6-cyclization product (**12b**) exclusively in 62% yield as a sole isolable product. Although only two have been tested, the present 1,6-cyclization route seemed to be comparable to the existed procedures[4,5] (Scheme 2).



Scheme 2

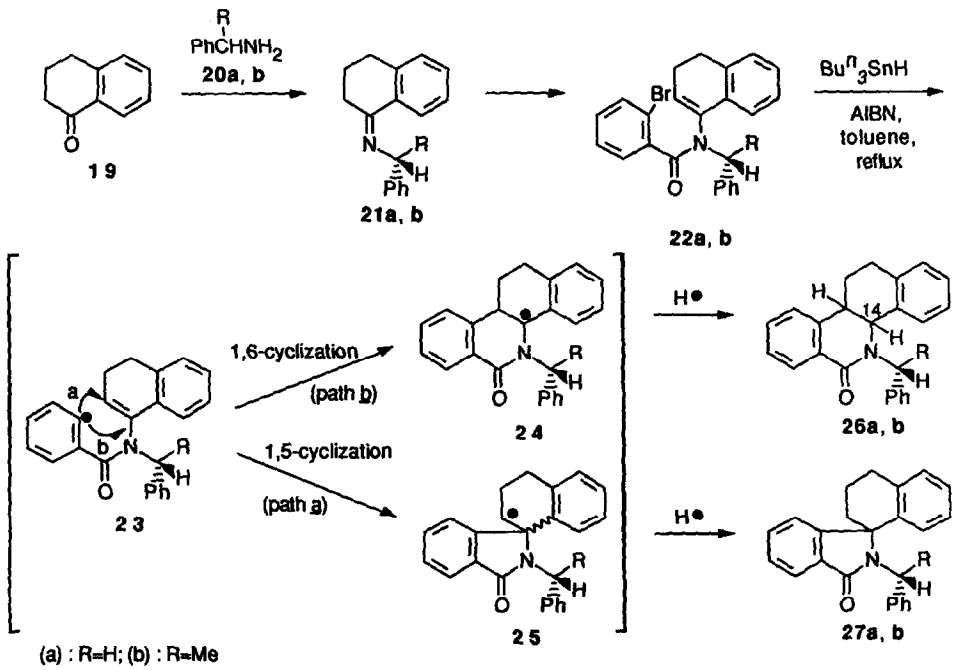
As the second group, the enamines, **15a** and **b**, prepared by the Bischler-Napieralski reaction[3] of the amides (**13a** and **b**), followed by exposure of the resulting salt **14a** and **14b** with ammonium hydroxide, respectively, were used as the substrates. Upon treatment with tri-*n*-butyltin hydride (2 equiv.) in boiling toluene in the presence of a catalytic amount of AIBN **15a** afforded again the 1,6-cyclization (path b) product (**18a**) exclusively in 51.3% yield as a sole isolable product. Similarly, **15b** formed the 1,6-cyclization product (**18b**), known as xylopinine,[6] in 31.9% yield as a sole isolable product (Scheme 3). Since both of the photochemical[4] and the palladium mediated[5] methods would not be able to furnish the cyclization products directly from the enamine substrate, the present method is more superior to those existed with respect to the preparation of the protoberberine type isoquinoline alkaloids.

The third group of the substrates bearing *endo*-olefin bond also afforded cyclization products under the same conditions. However, they did not show regioselectivity to give rise to a mixture of the products by competitive *endo*-1,6- (path b) and *exo*-1,5- (path a) cyclizations. Thus, the enamide (**22a**), prepared by treating the Schiff base (**21a**), generated from 1-tetralone (**19**) and benzylamine (**20a**), with 2-bromobenzoyl chloride (**8a**) in the presence of triethylamine gave the isoquinolone (**26a**) formed by 1,6-cyclization (path b) in 38.2% as a single epimer and the isoindolone (**27a**) formed by 1,5-cyclization (path a) in 27.3% yield. Stereochemistry of the B/C-ring juncture of the former compound was readily deduced to be *cis*-relationship based on



Scheme 3

comparison of coupling constant of 14-H (4.4 Hz) with that (4.3 Hz) of the established compound.[7] On the same treatment the optically active enamide (**22b**), prepared similarly using (*R*)-1-methylbenzylamine (**20b**), afforded the 1,6-cyclization (path b) product (**26b**) in 20% yield as a 2:1 diastereomeric mixture[8] and the 1,5-cyclization (path a) product (**27b**) in 20% yield as a 5:2



Scheme 4

diastereomeric mixture.[8] Stereochemistry of the B/C ring juncture of the former product was deduced similarly as above to have *cis*-relationship based on coupling constant of 14-H (4.6 Hz).[7] It was noteworthy that some extent of diastereoselectivity could be observed in the latter substrate reflecting the chirality of the amine moiety (Scheme 4). The diastereomeric isoquinolone (**26b**), after the reduction with lithium aluminum hydride, could be separated into consisting diastereomers, (+)-amine, $[\alpha]_D^{28}$ +151.58° (*c* 0.19, $CHCl_3$), and (–)-amine, $[\alpha]_D^{28}$ –214.12° (*c* 0.34, $CHCl_3$), by preparative tlc though whose absolute configuration could not be determined.

In conclusion it has now been demonstrated that the unfavorable *endo*-1,6-cyclization (path b) could exclusively occur in particular compounds bearing *exo*-olefin moiety such as the compounds belong to the first and the second groups, while competing *endo*-1,6-(path b) and *exo*-1,5 (path a)-cyclizations occurred in the compounds bearing *endo*-olefin moiety belong to the third group. The present observation may be useful for the construction of the protoberberine and the benzophenanthridine groups of the isoquinoline alkaloids.

References and Notes

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8. Ratio was estimated based on ^{1}H-nmr spectrum (500 MHz).

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