A SYNTHETIC APPROACH TO ERVITSINE — A GENERAL SYNTHESIS OF 2-INDOLYLPYRIDINE DERIVATIVES

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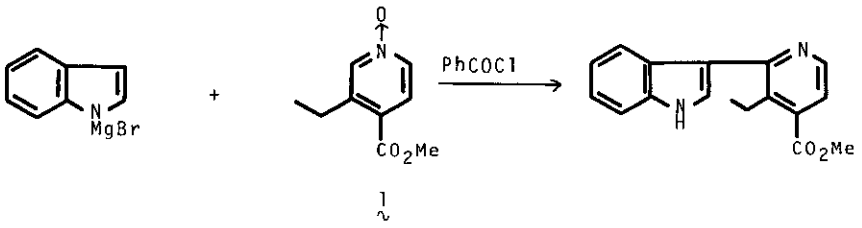
Abstract — Reactions of indolylmagnesium bromide and lithium diindolylcuprate with several pyridine N-oxides are described.

Several years ago[1], we reported a novel condensation reaction of indolylmagnesium bromide with pyridine N-oxide (1) and applied it to a stereoselective total synthesis of dasycarpidone (2).



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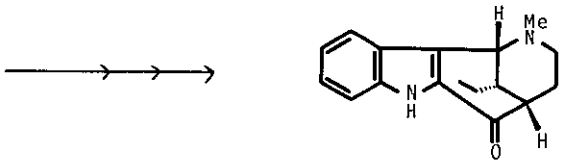

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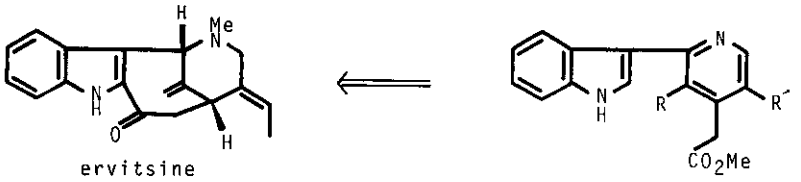
In subsequent work on the total synthesis of another 2-acylindole, ervitsine,[2] we required a method for the preparation of 2-indolyl-4-methoxycarbonylmethylpyridine

derivatives. We investigated the condensation reaction of indolylmagnesium bromide with several pyridine N-oxides under various conditions and also compared the reactivity of indolyl Grignard reagent versus lithium diindolylcuprate[3]. Typical experimental procedures are as follows.

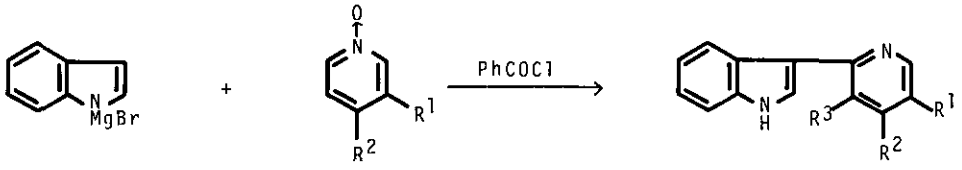


ervitsine

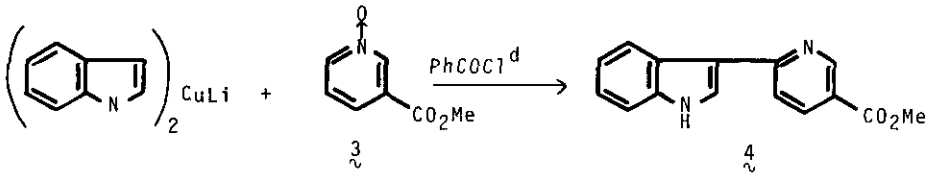
Firstly condensation reaction of indolylmagnesium bromide with 3-methoxycarbonylpyridine N-oxide was carried out. To an ice-cold solution of ethylmagnesium bromide (60 mmol) in dry THF (20 ml) was added dropwise a solution of indole (67 mmol) in dry THF (15 ml) over 30 min under nitrogen atmosphere. The mixture was stirred for 30 min at 0°C and then dry methylene chloride (60 ml) was added in order to obtain complete solution. After stirring for an additional 1.5 h at room temperature, the mixture was cooled to -20°C. To this was added dropwise a solution of pyridine N-oxide (3) (20 mmol) and benzoyl chloride (20 mmol) in dry methylene chloride (20 ml). The mixture was stirred for 2 h at -20°C, quenched with saturated ammonium chloride solution and diluted with chloroform. The organic layer was washed with brine, dried over magnesium sulphate and then evaporated. Purification of the resultant residue by silica gel column chromatography afforded the desired compound (4).

Secondly condensation reaction of lithium diindolylcuprate with 3-methoxycarbonyl-pyridine N-oxide was carried out as follows. Purified cuprous iodide (14 mmol) was placed in a round bottom flask. Nitrogen was intruduced into the apparatus and then dry ether (10 ml) was added to the flask. The mixture was cooled to -40°C and a solution of indolyllithium [prepared from indole (23 mmol) and n-butyllithium (23 mmol) in dry ether (10 ml)] was added dropwise with stirring over 20 min. The resultant dark blue solution was stirred for 2 h at -40°C. To that solution was added dropwise a solution of pyridine N-oxide (3) (3.9 mmol) and benzoyl chloride (3.9 mmol) in dry methylene chloride (4 ml) over 40 min and the mixture was stirred for an additional 2 h at -40°C, quenched with saturated ammonium chloride solution, washed with brine, dried over magnesium sulphate and then evaporated to leave a residue which was subjected to chromatography on silica gel to give the desired compound (4).

The results are summerized in Table I.



Conditions						
Indolylmagnesium bromide/ pyridine N-oxide (mole ratio)	Pyridine N-oxide[a]	Temp (°C)	Time (h)	Product	m.p. (°C)	Yield[b] (%)
2	3: R^1=CO_2Me, R^2=H	-10	2	4: R^1=CO_2Me, R^2=H, R^3=H	203∿206	12.5
2[c]	3: R^1=CO_2Me, R^2=H	-40	2	4: R^1=CO_2Me, R^2=H, R^3=H		12
3	3: R^1=CO_2Me, R^2=H	-10	2	4: R^1=CO_2Me, R^2=H, R^3=H		13.7
3	3: R^1=CO_2Me, R^2=H	-20	2	4: R^1=CO_2Me, R^2=H, R^2=H		17.6
1.2	5: R^1=Et, R^2=CH_2CO_2Me	-20	2	6: R^1=H, R^2=CH_2CO_2Me, R^3=Et		3
				7: R^1=Et, R^2=CH_2CO_2Me, R^3=H		5
3	5: R^1=Et, R^2=CH_2CO_2Me	-20	2	6: R^1=H, R^2=CH_2CO_2Me, R^3=Et		10.3
				7: R^1=Et, R^2=CH_2CO_2Me, R^3=H		16.9
3	8: R^1=Et, R^2=Me	-20	2	9: R^1=H, R^2=Me, R^3=Et	117∿119	3.8
				10: R^1=Et, R^2=Me, R^3=H	119∿120	21.4



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Conditions			Product
Lithium diindolylcuprate/pyridine N-oxide (mole ratio)	Temp (°C)	Time (h)	Yield (%)
3.5	-40	2	16
3[d]	-40	2	0
5	-40	2	14.9
10	-40	2	9.1

a) All of the pyridine N-oxides were prepared by heating the corresponding pyridine derivatives in a mixture of AcOH and H_2O_2 at 80°C.

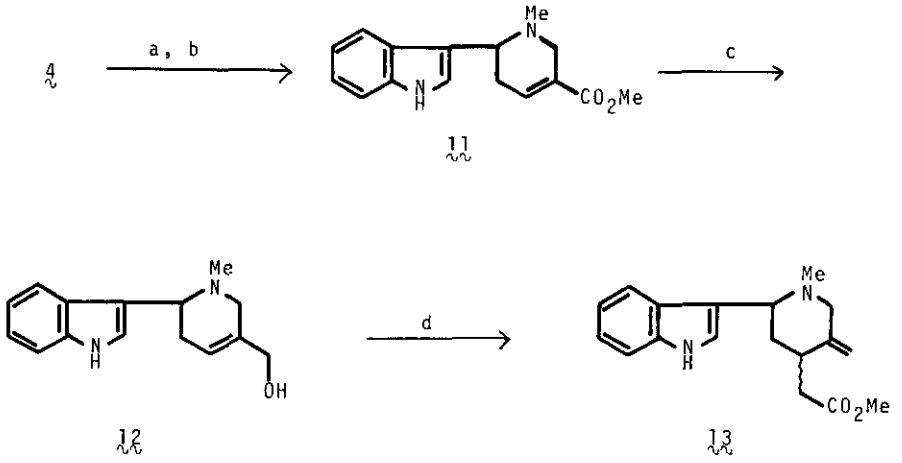
b) Isolated yield based on pyridine N-oxide used.

c) Catalytic amount of CuI was used.

d) When MeI was used instead of benzoyl chloride, none of the desired condensation product was obtained.

We then turned our attention to the synthesis of 2-indolyl-4-methoxycarbonylmethyl-piperidine derivatives which should be important intermediates in the synthesis of ervitsine and its analogues.

Thus, treatment of the compound (4) with methyl iodide followed by methanolic sodium borohydride reduction afforded the 4,5-dihydropiperidine (11). Lithium aluminium hydride reduction of the ester (11) in dry tetrahydrofuran gave the allyl alcohol (12)[4], mp 183 ∿ 185°. Orthoester Claisen rearrangement[5] provided an unseparable mixture of the homoester (13) (cis : trans = ca.1 : 1) in approximately 50 % yield.



a) MeI/MeOH, reflux b) $NaBH_4$/MeOH, r.t. c)$LiAlH_4$/THF, reflux
d) $CH_3C(OMe)_3$, $CH_3CH_2CO_2H$/Diglyme/160°, 10min.

Thus a general synthesis of 2-indolyl-4-methoxycarbonylmethylpiperidine derivatives, which may be key intermediates in the synthesis of ervitsine, has been accomplished. Although the yields in the condensation reactions described herein are unfortunately low, the method is nevertheless noteworthy in comparison with other known routes[6] to 2-indolylpyridine derivatives, which are not only lengthy but are also restrictive with regard to the introduction of synthetically useful functionality. To our knowledge, this paper also constituted the first report concerning the reactivity of lithium diindolylcuprate. The total synthesis of ervitsine according to this procedure is now under investigation in these laboratories.

REFERENCES and NOTES

1. T. Kametani and T. Suzuki, J. Chem. Soc. (C), 1971, 1053; Idem, J. Org. Chem., 1971, 36, 1291; Idem, Chem. Pharm. Bull. (Tokyo), 1971, 19, 1424.
2. M. Andriantsiferana, R. Besselièvre, C. Riche and H. P. Husson, Tet. Lett., 1977, 2587.
3. G. H. Posner, Org. Reactions, 1972, 19, 1.
4. This compound was also characterised as the acetate. IR 3460 and 1735 cm^{-1}.
5. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner, and M. R. Petersen, J. Amer. Chem. Soc., 1970, 92, 741 ; Y. Langlois and P. Potier, Tetrahedron, 1975, 31, 419; For a review, see F. E. Ziegler, Accs. Chem. Res., 1977, 10, 227.
6. A. Jackson, N. D. V. Wilson, A. J. Gaskell and J. A. Joule, J. Chem. Soc. (C), 1969, 2738; L. J. Dolby and H. Biere, J. Amer. Chem. Soc., 1968, 90, 2699; G. Büchi, S. J. Gould and F. Näf, J. Amer. Chem. Soc., 1971, 93, 2492.
7. All new compounds reported herein gave satisfactory elemental analyses or showed molecular ions in their mass spectra consistent with the proposed structures. In addition all spectral data were consistent with the assigned structures.

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