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THE INTERMOLECULAR BENZYNE CYCLOADDITION APPROACH TO DEHYDRONORAPORPHINES AND OXOAPORPHINES. TOTAL SYNTHESIS OF PO-3

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Abstract: The synthesis of dehydronoraporphines and oxoaporphines has been achieved by means of the convergent and highly regioselective intermolecular benzyne cycloaddition approach. The first total synthesis of the quaternary oxoaporphine PO-3 is described.

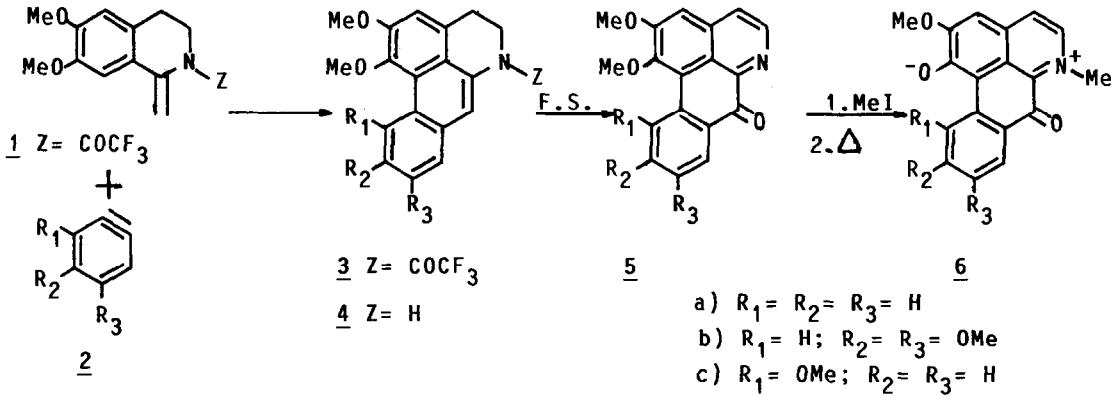
Recent reports[1] from our laboratory have stressed the validity of the intermolecular benzyne cycloaddition (inter BC) approach as a simple route to several types of aporphine alkaloids, namely, dehydronoraporphines, 4,5-dioxoaporphines and aristolactams. The most remarkable features of this versatile strategy for constructing the aporphine skeleton were found to be both its convergence and high regioselectivity.

Continuing with our efforts in this area we would like now to report the implementation of the inter BC approach for the synthesis of dehydronoraporphines and oxoaporphines. The total synthesis of the quaternary oxoaporphine alkaloid PO-3[2] is described for the first time.

Our synthetic plan (scheme 1) called for initial [4+2] cycloaddition of an adequately protected 1-methylene-isoquinoline 1 with the appropriate benzyne 2. N-deprotection of adducts 3 should then provide dehydronoraporphines 4,[3] which by subsequent oxidation should afford oxoaporphines 5,[3] easily convertible into the quaternary derivatives 6.

At the outset, several available protective groups[4] for the enamine of 1 were considered. Initial experiments with N-carbethoxy[5] and N-trifluoracetyl adducts 3 clearly showed the latter to be preferable (vide infra).

In the event, as expected, reaction (reflux DME, 2 hr) of the easily available N-trifluoracetyl-1-methylene-isoquinoline 1 ($Z=COCF_3$)[6] with the preformed benzenediazonium-2-carboxylate[7] precursor of 2a, or the "in situ"[8] prepared 2b, led uneventfully to [4+2] adducts 3a and 3b in 61% and 22% yields[9] respectively. The trifluoracetyl protective groups of 3a and 3b were then easily removed ($NaBH_4$/EtOH,R.T., 10 min.) yielding dehydronoraporphines 4a and 4b[10] in 75-85% yield. Final treatment of 4a and 4b with Fremy's salt[11] led to the naturally occurring lysicamine 5a (70% yield) and O-methyl-



SCHEME 1

atheroline 5b (65% yield).[9]

As a final test we decided to apply the above procedure to the synthesis of the rare quaternary oxoaporphine alkaloid PO-3 6c.[2] This was achieved,[9] as before, by cycloaddition (1+2c[8] → 3c, 26% yield), N-deprotection (3c → 4c, 90% yield), Fremy's salt oxidation (4c → 5c, 71% yield), treatment with MeI and final thermolysis[12] (5c → 6c[13], 50% yield).

To sum up, we have shown that the inter BC approach is a convergent and regioselective method for the synthesis of dehydronoraporphines,[3,5] oxoaporphines[3] and quaternary oxoaporphines.[3] Further work in progress will also show the versatility of this method for the synthesis of other isoquinoline alkaloids.

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10. Spectroscopic data identical with that reported in ref. 5.
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13. The IR and UV spectra of 6c are identical with those reported to the alkaloid PO-3 in ref. 2. Satisfactory NMR data (250 MHz,Cl_3CD+TFA, δ) were also obtained for 6c [8.61 (d, J=6.1, H-5); 8.41 (d, J=6.1, H-4); 8.13 (d, J=7.9, H-8); 7.72 (t, J=7.9, H-9); 7.57 (d, J=7.9, H-10); 7.5 (s, H-3); 4.71 (s, quaternary N-Me); 4.22 (s, OMe); and 4.17 (s, OMe)].

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