Tetrahedron Letters,Vol.29,No.20,pp 2491-2492,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE INTERMOLECULAR BENZYNE CYCLOADDITION (IBC) APPROACH TO PROTOBERBERINES. HIGHLY CONVERGENT SYNTHESIS OF 8-OXYPSEUDOPALMATINE

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Abstract.- C13-unsubstituted protoberberines can be synthesized by means of the IBC approach provided that a temporary blocking group is used in the key step. 8-Oxypseudopalmatine has been synthesized by this method.

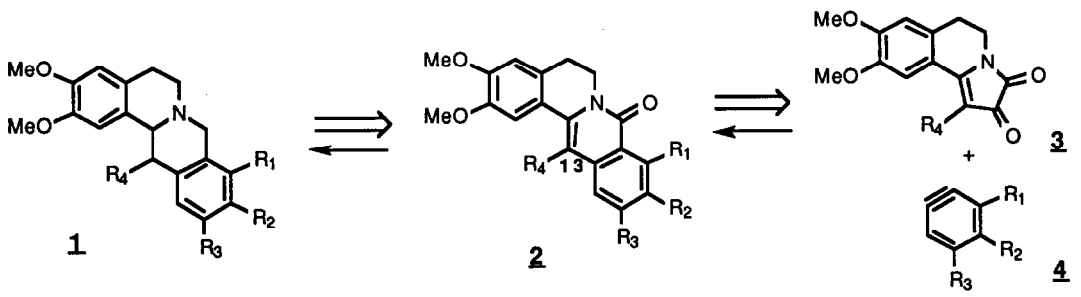
The protoberberine skeleton has been, and still is, an interesting target structure for synthetic chemists [1]. During our recent work on the use of arynes as synthetic reagents [2], it was discovered that the protoberberine skeleton could be assembled in a highly convergent manner by reacting isoquinolinepyrrolinediones (**3**) with arynes (**4**)[3]. Formally, this operation involves a [4+2] cycloaddition followed by cheletropic extrusion of carbon monoxide, though there is so far no proof that this really is the mechanism involved.

The above key step was the cornerstone of our recent synthesis of (±)-corydaline (**1a** R_4=Me), which was easily prepared in a regioselective manner starting from pyrrolinedione **3**, (R_4=Me) and the unsymmetrically substituted aryne **4a**[3]. In spite of this success, all attempts to prepare the most common, C13-unsubstituted members of the protoberberine family by reacting pyrrolinediones **3** (R_4=H) with arynes **4** met with failure [3], as an unexpected arylation reaction produced the undesired aryl substituted compounds **2** (R_4=Ar).

We now report that C13-unsubstituted protoberberines **1** (R_4=H) can be efficiently prepared by the IBC approach [2], provided that a removable blocking group (a halogen) is placed at C-13 (protoberberine numbering) to suppress the undesired arylation.

We initially prepared chloroisoquinolinepyrrolinedione **3** (R_4=Cl) by the standard method [3,5]; reaction of this precursor with unsubstituted benzyne (**4b**) generated by the thermal decomposition of preformed benzenediazonium-2-carboxylate[4] yielded the expected adduct **2b** (R_4=Cl) in 48% isolated yield (Scheme 1). It was subsequently found more convenient to prepare bromo-blocked pyrrolinedione **3** (R_4=Br) by direct bromination (CH_2Cl_2, Br_2, r.t., 98%) of easily available **3** (R_4=H); its reaction with benzyne as above provided 13-bromo-8-oxyprotoberberine **2b** (R_4=Br) in 54 % isolated yield[5] and subsequent hydrogenolysis (H_2, 10% Pd/C, 30 psi, 1 hr) readily afforded oxyprotoberberine **2b** (R_4=H) in 98% yield [5,6].

As a final test we applied the above highly convergent methodology to the synthesis of 8-oxypseudopalmatine **2c** (R_4=H), a minor alkaloid recently isolated from Stephania suberosa[7].



a R_1=R_2=OMe, R_3=H **b** R_1=R_2=R_3=H **c** R_1=H, R_2=R_3=OMe

Scheme 1

Bromoisoquinolinepyrrolinedione **3** (R_4=Br) was reacted with the symmetrically substituted benzyne **4c** generated as before by thermal decomposition of the preformed diazonium salt. The expected 8-oxyprotoberberine **2c** (R_4=Br) was isolated in 24% yield by extensive chromatography, and hydrogenolysis gave 8-oxypseudopalmatine **2c** (R_4=H) in 96% yield. The physical and spectroscopic properties (UV, IR, 1H-NMR, MS) of our synthetic compound were completely identical with those reported for **2c** (R_4=H)[7,8]. This total synthesis represents also a formal synthesis of xylopinine **1c** (R_4=H)[8a].

In view of the high regioselectivity of intermolecular benzyne cycloaddition of unsymmetrically substituted arynes[2,3], it can be safely concluded that the methodology described above should be applicable to the unambiguous synthesis of both 9, 10 and 10, 11 substituted protoberberines.

Acknowledgements.- This work has been supported by the CAICYT (Spain). We thank Prof. M. Shamma for sending a copy of de PMR spectrum of 8-oxypseudopalmatine .

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(Received in UK 21 March 1988)