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2-(o-Tolyl)-4,4-dimethyl-2-oxazolines - A New Vehicle for Facile Convergent Synthesis of Protoberberine Alkaloids

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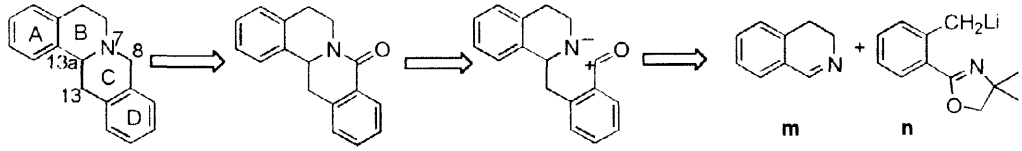
Abstract: A single step synthesis of 8-oxotetrahydroprotoberberines (57-82%) by the addition of lithiated 2-(o-tolyl)-4,4-dimethyl-2-oxazolines on 3,4-dihydroisoquinolines is described.

The antiinflamatory, antimicrobial, antileukemic and antitumor properties[1] of protoberberine alkaloids - tetracyclic systems with an isoquinoline core, have led to considerable efforts in development of their synthetic methodologies. The synthetic approaches available in literature are generally plagued by non-availability of starting materials, non-regiospecific synthesis, multistep procedures and moderate to poor yields[2].

A retrosynthetic analysis (scheme - 1) reveals that the sequential cleavage of N7-C8 and C13-C13a bonds gives 3,4-dihydroisoquinoline (**m**) and o-substituted aryl ring with one electrophilic and one nucleophilic centre (**n**). We envisaged that the presence of 2-oxazoline unit on toluene at o- position would not only facilitate the generation of benzylic anion but also facilitate the intramolecular cyclisation of the intermediate addition product to provide protoberberine skelton in a single step. Here we report that 2-(o-tolyl)-4,4-dimethyl-2-oxazolines (**1**) on lithiation at 0°C undergo addition on 3,4-dihydroisoquinolines (**3**) to provide **6** and subsequent reductions with LAH give protoberberine alkaloids 7 (57-78%).



Scheme -1

Treatment of **1a** with n-butyl lithium in ether at 0°C for 30 min results in the formation of a deep red coloured anion, which on addition of 3,4-dihydroisoquinoline (**3a**) and subsequent acidic work-up provides **6a** (78%), m.p. 166-68 (lit.[3] m.p.169-70°C)[7], MS m/z 249(M^+, 68). This reaction mixture on NH_4Cl work-up and purification over NEt_3 deactivated silica gel provides **5** (R = R_1 = R_2 = H), MS m/z 320

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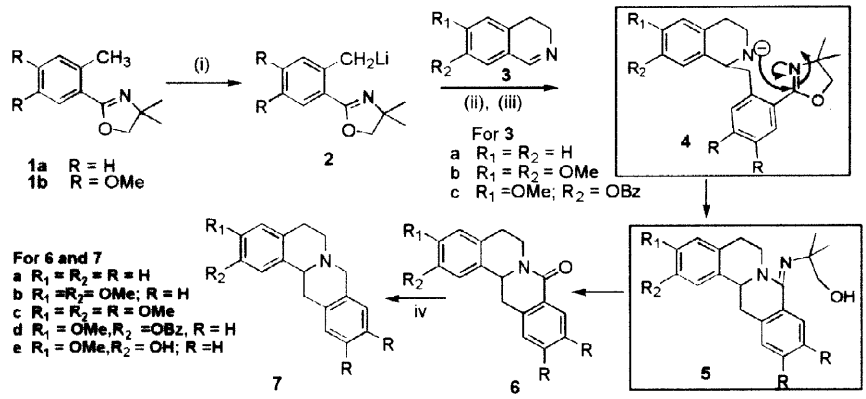
(M$^+$, 1). Its ^{1}H nmr exhibits C-13aH at δ 4.26, along with other signals due to protoberberine and aminoalcohol units. On addition of D_2O and keeping the sample overnight, the signal due to C-13aH shifts to δ 4.90 the normal position for **6a**. These results show that **2a** adds to **3a** to give intermediate **4** which subsequently adds to oxazoline C=N to give **5** and during acidic work-up is hydrolysed to provide **6a**. Therefore, addition of **2a** on **3a** provides a single step synthesis of (±) 8-oxoprotoberberine **6a** (78%).



Reaction conditions (i) n-BuLi -Et_2O, 0°C, 30 min. (ii) 0°C, 30min, RT 12h (iii) EtOH-H_2SO_4, stir 30 min.(iv) $LiAlH_4$ - THF, reflux, 2h

Scheme - 2

Similarly, the addition of anion derived from **1a** with **3b** and **1b** with **3b** and **3c** provide respectively alkaloids **6b** (82%), m.p. 143-44 (lit.[4] m.p. 143-45°C), MS m/z 309(M$^+$,100); **6c** (58%), m.p.187-88 (lit.[4] m.p. 188-89°C), MS m/z 369(M$^+$, 48) and **6d** (78%), m.p. 152-54°C, MS m/z 385(M$^+$, 31). The compounds **6b** and **6c** on reduction with LAH and **6d** on reduction with LAH and subsequent debenzylation with EtOH - HCl provide respective alkaloids **7b** (68%), m.p.HCl 236-37 (lit.[6] mp 236-38°C), MS m/z 295 (M$^+$, 29); **7c** ((±)xylopinine, 76%), m.p.141-42 (lit.[4] mp. 142-43°C), MS m/z 355 (M$^+$, 35) and **7e** ((±)bharatamine, 65%), m.p. 180-82 (lit.[5] m.p. 182-83°C), MS m/z 281 (M$^+$, 100).

Thus, 2-(o-tolyl)-4,4-dimethyl-2-oxazolines (**1**) are excellent vehicles for the convergent synthesis of protoberberine alkaloids where benzylic anions are generated at a more practicable ice bath temperature and both addition and cyclisation steps are acheived in a concerted manner. The use of easily available chiral oxazoline rings in **1** may provide a facile enantioselective synthesis.

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