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Photochemical Synthesis of 7,8-Dioxygenated Isoquinoline Alkaloids

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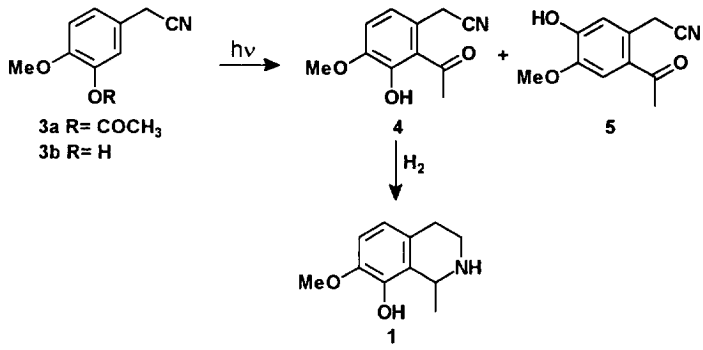
Abstract: A new approach to the synthesis of 7,8-dioxygenated tetrahydroisoquinoline alkaloids based on the photo-Fries rearrangement of esters derived from 3-hydroxy-4-methoxy phenylacetonitrile is reported. The procedure was applied to the synthesis of the alkaloid Arizonine and 1-benzyl tetrahydroisoquinoline precursor of cularine and 1,2-berbine alkaloids.

Isoquinoline nuclei bearing oxygen functions at positions 7 and 8 are commonly present in many alkaloid types including simple isoquinolines, 1-benzylisoquinolines, cularines, quettamines, berbines and benzophenanthridines.[1] Synthesis of their tetrahydro derivatives is hindered by the substitution pattern of the aromatic ring. The Bischler-Napieralsky reaction of a 3,4-dioxygenated phenylethylamide is regioselectively unfavourable at the cyclization step, so some protection-deprotection or activation strategy is usually required to obtain the desired regioisomer.[2] The Pomerantz-Fristch reaction and its modifications are more useful in this context,[2d,3] particularly for the preparation of Reissert compounds as synthetic intermediates for more complex molecules;[4] however, the process involves many steps and yields are usually quite modest. Regioselective metalation of ß-(3,4-dialkoxyphenyl)ethylamines gives acceptable yields of 7,8-dialkoxy-3,4-dihydroisoquinolines, but with a major drawback: no benzyl groups can be directly introduced at C-1 owing to the acidity of the benzyl protons in the electrophile.[5]

A synthetic approach based on ring formation by linking C-1 to the nitrogen atom in the last step,[6] (thus requiring a 1,2,3,4-tetrasubstituted aromatic system) was developed. As shown elsewhere,[7] one such system can be constructed by photo-Fries rearrangement[8] of an appropriately trisubstituted benzene derivative. This paper reports a preliminary account of the application of this approach to the synthesis of the isoquinoline alkaloid (±)-arizonine (**1**) and its extension to a practical, expeditious preparation of several 1-benzyl-7-methoxy-8-hydroxy tetrahydroisoquinolines (**2a-c**).

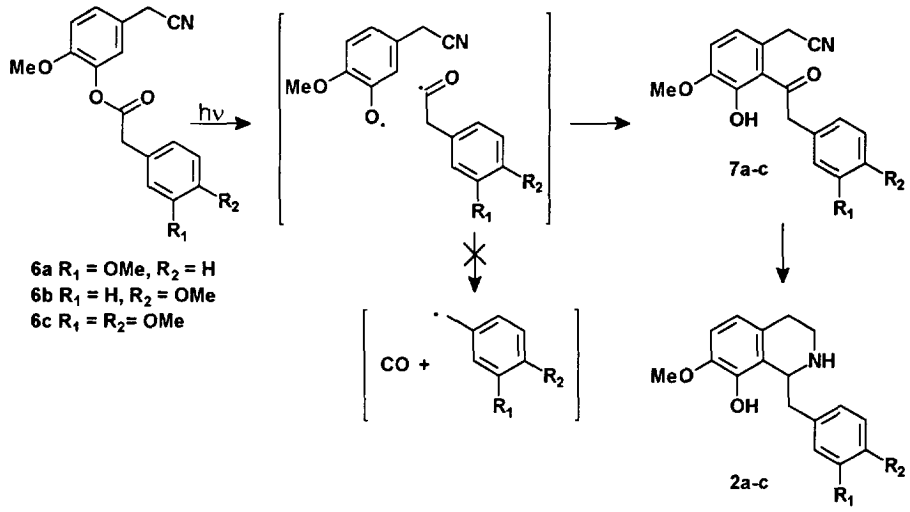
Acetate **3a** was selected because the cyanomethyl group proved to be inert under the irradiation conditions[9] used; also its small size avoids the adverse steric effect of bulky substituents at C-5[7] and the molecule contains a nitrogen atom at an appropriate position for ring formation. Phenol **3b** was synthesized from protected isovanillin[10] by using the $NaBH_4/SOCl_2/KCN$ sequence, followed by deprotection and acetylation.[11] When isovanillin was protected as a benzylether,

deprotection with HCl/EtOH was invariably accompanied by solvolysis of the cyanide. In this respect, tosylate proved to be another efficient protecting group, and deprotection (KOH/MeOH) left the nitrile function untouched.



Compound **3a** was irradiated at 254 nm (Vycor glass) under various conditions. In a homogeneous MeOH/H_2O solution, **4** was isolated with a 55% yield, together with the corresponding *para*-isomer, **5**, (11%) and phenol **3b** (16%).[12] Analogous results were obtained by irradiating **3a** in a micellar solution (SDS as surfactant) with an occupancy mean number from 0.5 to 3. As expected,[7] the *ortho/para* ratio was dramatically improved when a hexane slurry of **2a** included into NaX or NaY zeolites was irradiated (23-30% *ortho*, <1% *para*); however, the long irradiation time required, the difficulties encountered in recovering the irradiation products (recoveries never exceeded 60%) and the amount of phenol formed (24-31%) limit the synthetic use of this procedure. Catalytic hydrogenation of the rearranged acetophenone **4** (PtO_2, in EtOH/HCl) afforded the target alkaloid (±)-arizonine (**1**) in a 80% yield (35% yield from isovanillin).[13]

Extending this approach to the synthesis of 1-benzyl-7,8-dioxygenated tetrahydroisoquinolines, entailed irradiating the corresponding phenylacetates. Based on the radical mechanism accepted for the photo-Fries rearrangement,[14] one additional process could be anticipated as a result of the phenylacetyl radical produced, which is known to easily undergo decarbonylation, as in the photolysis of dibenzylketone.[15] Because of their low solubility in MeOH/H_2O, irradiation of phenyl acetates **6a-c** was carried out in *t*-BuOH/H_2O/THF (7:7:2 v/v), a solvent mixture combining appropriate polarity, viscosity and a low hydrogen donor capability, minimizing phenol formation and giving rise to the best *ortho/para* ratio. Under these conditions, the crude reaction mixture provided a good yield of *ortho*-hydroxyketones **7a-c** (72-78%), and low concentrations of the *para*-isomers (8-14%) in addition to phenol **3b** (14-16%). In any case, some products resulting from decarbonylation of the phenylacetyl radical were detected, so the rate of the primary photoprocess from S_1, leading to singlet birradical formation (and recombination) should be much faster than intersystem crossing to T_1, thereby excluding the possibility of the corresponding triplet birradical,from which the decarbonylation process is known to readily occur, being produced.[16]



Although the *ortho* rearrangement was quite efficient, chromatographic purification of **7a-c** resulted in substantial losses of the product. In order to circumvent the purification step, the hydrogenation was conducted on the photochemical crude, and the desired isoquinoline (**2a-c**) product crystallized from the mixture. The yields of pure products **2a-c** were not too high (32-38%) in spite of the fact that the hydrogenation crudes accounted for over 60% of the 7,8-substituted isoquinolines as shown by ^{1}H-NMR.

Compound **2c** is the key intermediate in the total synthesis of the 1,2-berbine alkaloid (±)-caseadine, and has been prepared in a low yield (< 5%) by Kametani using the Bischler-Napieralsky approach.[2c] Compounds **2a** and **2b** are interesting precursors for ring-D modified cularine alkaloids, which exhibit papaverine-like activity, although by a different mechanism.[17]

This synthetic method is a convergent alternative route to the synthesis of isoquinoline nuclei oxygenated at positions 7 and 8. The possibility of combining this strategy with enantioselective catalytic hydrogenation to accomplish the asymmetric synthesis of 1-benzylated tetrahydroisoquinolines is currently under study.[18]

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11. All compounds exhibited satisfactory microanalytical and spectroscopic properties. Physical properties of the new compounds: (**3a**): 60-62°C; (**6a**) and (**6b**): oils, solidified on standing; (**6c**): 90-92°C; (**4**): 128-129°C; (**5**): 150-151°C; (**1**, as salycilate): 206-208°C (lit[2d] 208-210°C), (**7a**): oil; (**7b**): 126-127°C; (**7c**): oil; (**2a**, as hydrochloride): 198-200°C; (**2b**, as hydrochloride); 152-153°C; (**2c**): 191-192°C.
12. In a typical run, a degassed (N_2) solution of **3a** (1.085 g, 5.3 mmol) in $MeOH/H_2O$ (2:1, 160 ml), was distributed among four Vycor tubes that were placed at the center of a cylindrical photochemical reactor equipped with eight low pressure Hg lamps (Sylvania G8T5). The reaction was monitored by GC/MS and allowed to proceed up to >90% conversion. The reaction mixture was separated by vacuum chromatography (Silica gel, CH_2Cl_2).
13. Alternative synthesis of (±)-**1** *via* Bischler-Napieralsky reaction, also starting from isovanillin, or *via* Bobbit cyclization starting from *o*-vanillin resulted in much lower yields. See ref. 2d.
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