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Short note

Reactivity of benzyl radicals: The trapping of primary, secondary and tertiary benzyl radicals with heterocyclic bases

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ABSTRACT

A photochemical benzylation of protonated quinolines was realized by single electron transfer (SET) to the excited state of the quinoline from the aromatic reactant. The benzylated product is formed by cross-coupling between the benzyl radical and the heterocyclic radical when they are in close proximity to one another. This allows the formation of products which are, to the best of our knowledge, unaccessible in other ways and which have now been obtained for the first time.

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1. Introduction

A recent paper devoted to the determination of the oxidation potentials of a series of substituted toluenes and biphenyls evidenced the possibility of an electron transfer from alkylbenzenes to excited N-methylquinolinium ions [1]. Since in the course of our research on the photochemical reactivity of quinolines [2] interesting reactions were obtained with alkylbenzenes, the above cited paper prompted us to undertake a rationalization of these results.

2. Experimental

2.1. Reagents, apparatus and methods

All the reagents and solvents were purchased by Sigma–Aldrich and were used as received.

The solutions were irradiated through Pyrex glassware in a Rayonet RPR-100 reactor, equipped with 16 interchangeable lamps, selectively emitting at 366 nm, and an internal merry-go-round apparatus for the homogeneous exposure of the samples to light.

GC–MS analyses were performed with an Agilent 6890 series gas-chromatograph equipped with a HP-5 MS 30 m capillary column, 0.25 mm i.d., 0.25 μm film thickness and a MS 5973N mass spectrometer detector.

^{1}H NMR analyses were performed with a Bruker Advance 500 spectrometer operating at proton resonance frequency of 500 MHz; the products were dissolved in a suitable deuterated solvent and TMS was added as internal reference.

2.2. Photochemical reactions

To a solution of the selected base (20 mmol), dissolved in acetonitrile (100 mL) in a Pyrex vessel and protonated with p-toluensulfonic acid (100 mmol), the benzyl derivative (200 mmol) and 30% aqueous hydrogen peroxide (120 mmol) were added. The solution was stirred with a magnetic stirrer in open air and irradiated for 16 h at 366 nm. At the end of the irradiation the solution was treated with an aqueous solution of $FeSO_4$ to destroy the excess of hydrogen peroxide and of any organic peroxide that may have formed during the irradiation. Acetonitrile was removed under vacuum, the remaining water solution was alkalinized and extracted with CH_2Cl_2. The solvent was dried and the organic solution was analysed via GC–MS; the products were separated via column chromatography on silica gel Si 60 40–63 μm with n-hexane:ethyl acetate (80:20) as eluent.

2 benzyllepidine **(4a)** [3] and 4-benzylquinaldine **(5a)** [4] are known products.

2-(1-Phenylethyl)-lepidine **(4b)**: oil, ms 247 (M^+), 246, 232, 217; ^{1}H NMR: 1.79(d, 3H), 2.60 (s, 3H), 4.47 (q, 1H), 7.04 (s, 1H), 7.20 (t,

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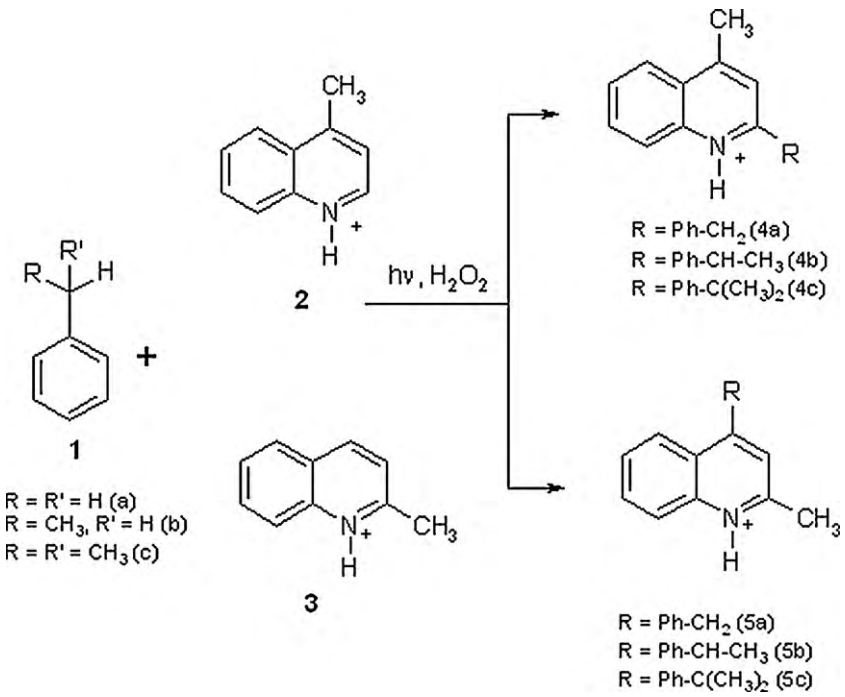


Scheme 1.

1H), 7.30 (t, 2H) 7.35 (d, 2H), 7.51 (t, 1H), 7.68 (t, 1H), 7.92 (d, 1H), 8.12 (1H); IR (nm): 2924, 2853, 2360, 2342, 1734, 1653, 1601, 1559, 1541, 1508, 1456, 1375, 1229, 758, 699.

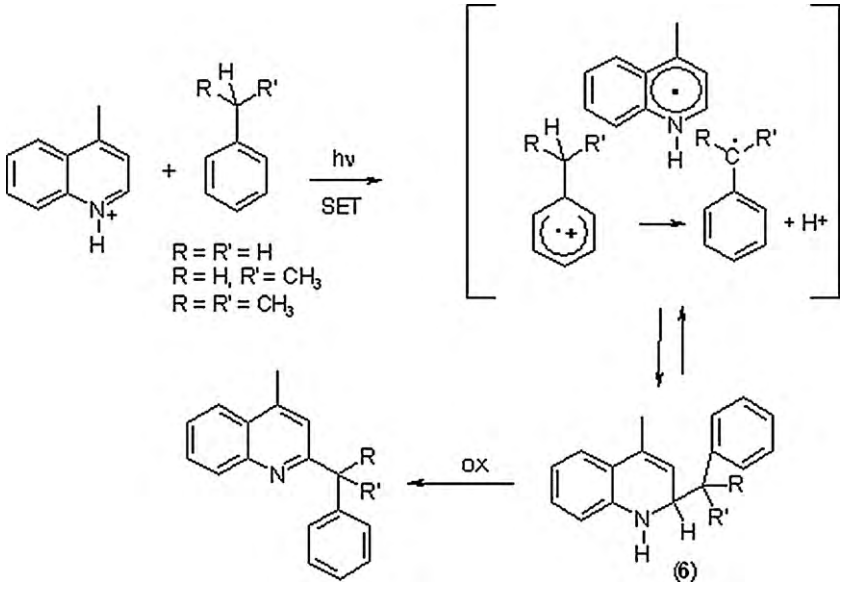
4-(1-Phenylethyl)-quinaldine **(5b)**: oil, ms 247 (M^+), 232, 217; ^{1}H NMR: 1.80 (d, 2H), 2.75 (s, 3H), 4.85 (q, 1H), 7.22 (m, 3H), 7.30 (m, 1H), 7.48 (m, 1H), 7.63 (t, 1H), 7.86 (t, 1H), 7.99 (d, 1H), 8.18 (d, 1H), 8.15 (d, 1H); IR (nm): 2994, 2853, 2360, 1734, 1600, 1508, 1457, 1376, 1233, 761, 701.

2-(1-Methyl,1-phenylethyl)-lepidine **(4c)**: oil, ms: 261(M^+), 260, 246, 231; ^{1}H NMR:1.88 (s,6H), 2.52 (s, 3H), 6.93, (s,1H), 7.20 (m,1H), 7.30 (m,4H), 7.53 (t, 1H), 7.70 (t,1H), 7.94 (d,1H), 8.15 (d,1H); IR (nm): 2924, 2853, 1731, 1603, 1560, 1494, 1448, 1377, 1261, 1095, 1030, 759, 699,569.

4-(1-Methyl,1-phenylethyl)-quinaldine **(5c)**: ms: 261 (M^+), 246, 231. The low yields of this product were not sufficient to obtain a clean sample for recording good quality ^{1}H NMR and IR spectra.

3. Results and discussion

In the reactions under investigation, acetonitrile solutions of toluene (**1a**), ethylbenzene (**1b**) or cumene (**1c**) were irradiated with 366 nm UV light in the presence of the protonated bases lepidine (**2**) or quinaldine (**3**) with the purpose of generating benzyl radicals by SET from the excited protonated heteroaromatic base, and then trapping these radicals by using the heteroaromatic base itself as spin trap (Scheme 1) [5].



Scheme 2.

In the literature concerning benzyl radical attack onto heteroaromatic bases, [6] oxidation and dimerization products of the benzyl radical are usually detected as by-products. In these cases, however, the benzyl radical is generated in the presence of the protonated heteroaromatic bases by an independent hydrogen abstraction system, such as e.g. a peroxide/metal ion redox chain. Therefore, it must diffuse in the medium to meet the heteroaromatic substrate; besides, the attack is highly reversible due to the relative stabilization of benzyl radicals.

Under the conditions employed in this work, (see Section 2) in the first runs with excess H_2O_2 no dimer was detected. This was ascribed to the fact that the two radicals are formed simultaneously and in close proximity by SET (Scheme 2), so that the reaction should not, in this case, be described as an attack of a free radical onto a protonated heteroaromatic base, to give an intermediate radical, but as a cross-dimerization of two radicals to give a paired electron intermediate, which is then rearomatized by H_2O_2 oxidation to give the benzylated product.

Therefore, since there is no diffusion of benzyl radicals in solution, as long as the oxidation of intermediate (**6**) (Scheme 2) is efficient, the dimer will not be formed.

Due to its relatively low stability, it is reasonable to consider the possibility that the non-aromatic intermediate (**6**) may revert back to the two parent radicals if it does not undergo immediate oxidation. As the concentration of the oxidant gets lower during the course of the process the benzyl radical could actually be regenerated from (**6**) by C–C bond breaking, then diffuse in solution and dimerize to a bibenzyl by-product. To verify this hypothesis, some reactions were realized at lower amount of hydrogen peroxide.

Indeed, the formation of the dibenzyl was detected in these cases, and it is interesting to compare the molar ratios benzylheterocycle/bibenzyl with the corresponding ratios found by Minisci under free-radical conditions [6]. In the case of lepidine we found 0.8 (reported 1.2) and for quinaldine we found 0.7 (reported. 0.13). The differences among the two processes are not surprising in view of the lower reversibility of the reaction described here, compared to the Minisci one, whose intermediate is a radical species, while intermediate (**6**) is not.

The benzylquinoline moiety may be found in the structure of naturally occurring alkaloids, widely studied for their biological properties, e.g. antimalarial activity [7,8]. Considering this, the described reaction may provide a synthetic strategy bringing, in just one step, to benzylated heteroaromatic bases, while known ionic processes require several steps [9]. Besides, this benzylation takes place not only with toluene but also with ethylbenzene and cumene, yielding products with a secondary and respectively tertiary benzyl substituent. These products, **4b**, **4c** and **5b**, **5c**, were never before described, to the best of our knowledge, probably owing to the difficulty of both ionic and radical attack of such a hindered and stabilized moiety, together with the ease of subsequent benzylic oxidation. This side process would be even more easy for a doubly benzylic position, so that such benzylated products would be quite labile even in mildly oxidizing environments.

Table 1
Yields of the benzylation products.

Heterocyclic base	(Product) Yield %		
	(**1a**)	(**1b**)	(**1c**)
(2)	(**4a**)2	(**4b**)8	(**4c**)1[a]
(3)	(**5a**)22	(**5b**)18	(**5c**)6

[a] Ref. [6].

The tertiary benzyl substituent has an advantage over the simple benzyl, in that products such as **4c** and **5c** cannot undergo benzylic oxidation. The yields relative to all the benzyl derivatives **4a–c** and **5a–c** are reported in Table 1.

Besides the above discussed intrinsic difficulties connected with attack of the cumyl radical, it was particularly surprising to find out even a small quantity of product **5c**, since cross-dimerisation of tertiary radicals in position 4 of quinaldine is usually not observed, probably due to steric hindrance by the hydrogen atom in position 5. [10] Furthermore, even in radical attack, substitution by tertiary radicals is never observed in that position [11]. This reaction could then be of interest from a synthetic standpoint; work is in progress in order to try to improve the yields.

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