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An efficient method for the preparation of antitumoral α-keto-imines benzyldihydroisoquinolines by selective benzylic oxidation with C/Pd in acetonitrile

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Abstract—A series of potent antitumor α-keto-imine BDHIQ derivatives were synthesized and assayed in vitro against L1210 leukemia cell line. A new and easy method for the direct formation of α-keto-imine from imine BDHIQ's was performed with 10% C/Pd in acetonitrile.

In order to prepare α-keto-imine 1-benzyldihydroisoquinolines (BDHIQ), several oxidation methods of imines have been described.[1–7] These methods include the spontaneous oxidation of benzylic carbons,[1,2] the photooxidation by exposition to singlet oxygen[3,4] and the oxidizing reagent treatments such as lead tetracetate, manganese dioxide, and diacetoxyiodobenzene.[5–7] The keto-imines prepared by these procedures were obtained in a variable yield.[1–7]

We have prepared a series of α-keto-imine BDHIQ's, as a new class of antitumor compounds with in vitro potent effect against L1210 leukemia cells. This activity was also reflected by their ability to perturbate the cell cycle inducing an accumulation of cells in the G1 phase.[8] This phase is an important period where various complex signals interact to decide a cell's fate: e.g. proliferation, quiescence, differentiation or apoptosis.

The preparation of the title compounds was accomplished at room temperature during 1 h in dry acetonitrile over 10% C/Pd.[9] Under these conditions the imines-BDHIQ's (**I**)[10–14] were directly transformed into α-keto-imines (**II**) in a good yield (see Scheme 1).[15] It is interesting to note, that the total oxidation of the dihydropyridine cycle of the BDHIQ was not observed by this procedure; so, oxidation at the *exo* benzylic carbon is faster than at the *endo* position of the heterocycle. The α-keto-imines obtained were stored as their salt forms.

This method, for the preparation of α-keto-imines (**II**), was applied to a series of BDHIQ's with several substitution patterns, both in the dihydroisoquinoline and the benzylic rings. The α-keto-imines obtained from an unsubstituted benzylic ring were furnished in typical 90% yields (compounds **II1** to **II15**). However, when the BDHIQ's mono or disubstituted on the benzene ring of the benzylic moiety were treated by the same reagents for 3 h, the corresponding α-keto-imines (compounds **II16** to **II26**) were obtained in a lesser yield.

The α-keto-imine BDHIQ's obtained (compounds **II**), were easily identified by ^{1}H NMR due to both characteristic systems, a dd deshielded signal at about δ 8.0 (H-2′ and H-6′), corresponding to two of the aromatic benzylic protons affected by the anisotropic effect of the carbonyl group, and an A_2B_2 system, at about δ 3.90 and δ 2.75, corresponding to the methylenes placed on the dihydroisoquinoline moiety (CH_2-3 and CH_2-4).

Indeed, the absence of the benzylic methylene in compounds **II** can be determined by NMR spectra[16] and confirmed by the presence of the characteristic ketone carbon signal at about 194 ppm.

Keywords: α-keto-imines; benzyldihydroisoquinolines; C/Pd, acetonitrile; selective oxidation; antitumoral.

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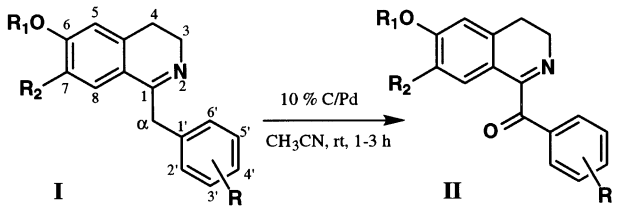
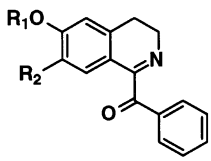
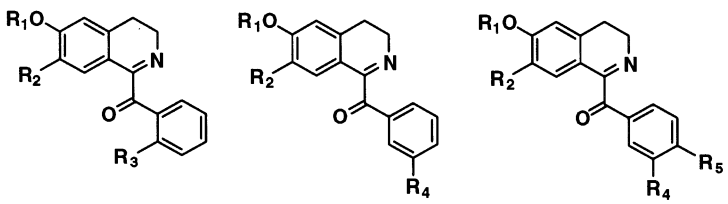




1: R_1= CH_2Ph; R_2= OCH_3
2: R_1= CH_2CH_3; R_2= OCH_3
3: R_1= $CH_2CH(CH_3)_2$; R_2= OCH_3
4: R_1= $CH_2CH{=}C(CH_3)_2$; R_2= OCH_3
5: R_1= CH_2Ph-*p*-OCH_3; R_2= OCH_3
6: R_1= $(CH_2)_4CH_3$; R_2= OCH_3
7: R_1= $CH_2CH{=}CHCH_3$; R_2= OCH_3
8: R_1= CH_3; R_2= OCH_2Ph
9: R_1= CH_3; R_2= $O(CH_2)_4CH_3$
10: R_1= CH_2Ph; R_2= H
11: R_1= $CH_2CH{=}C(CH_3)_2$; R_2= H
12: R_1= $CH_2CH(CH_3)_2$; R_2= H
13: R_1= $(CH_2)_4CH_3$; R_2= H
14: R_1= $CH_2CH{=}CHCH_3$; R_2= H
15: R_1= $(CH_2)_4COOCH_3$; R_2= H



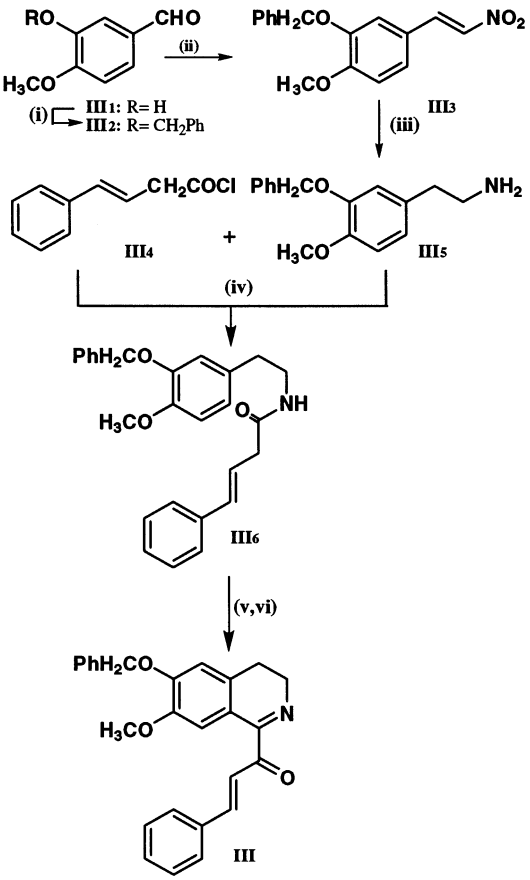
16: R_1= CH_2Ph; R_2= OCH_3; R_3= OTs
17: R_1= CH_2Ph; R_2= R_3= OCH_3
18: R_1= CH_2Ph; R_2= H; R_3= OCH_3
19: R_1= CH_2Ph; R_2= OCH_3; R_4= OAc
20: R_1= CH_2Ph; R_2= OCH_3; R_4= OTs
21: R_1= CH_2Ph; R_2= R_4= OCH_3
22: R_1= CH_2Ph; R_2= H; R_4= OCH_3
23: R_1= CH_2Ph; R_2= OCH_3; R_4= H; R_5= OH
24: R_1= CH_2Ph; R_2= R_4= H; R_5= OCH_3
25: R_1= CH_2Ph; R_2= R_4= R_5= OCH_3
26: R_1= CH_2Ph; R_2= H; R_4= R_5= OCH_3

Scheme 1.

This procedure has also been applied to the preparation of a new type of *trans*-styryl isoquinolines (**III**) (see Scheme 2). The acetoamide (**III6**) was prepared from isovanillin (**III1**) by a classic methodology,[11–14] including the Schotten–Baumann condensation between a phenylethylamine (**III5**) and the corresponding *trans*-styryl acetyl chloride (**III4**). Under these reaction conditions, **III6** was obtained in an overall yield of 50%. The synthesis of the subsequent α-keto-imine *trans*-styryl dihydroisoquinoline (**III**) was performed in an 'one-pot' sequence in two steps. The acetamide (**III6**) was first refluxed in CH_2Cl_2 in the presence of $POCl_3$, in a cyclodehydratation Bischler–Napieralski experiment. The reaction mixture was directly treated in acetonitrile by 10% C/Pd, and 5% NH_4OH. Because this type of conjugated styryl keto-imine is very unstable this reaction was carried out for 30 min only. After sephadex purification, compound **III** was obtained in 10% yield, but 50% of the starting material **III6** was also obtained (Scheme 2).

All the α-keto-imines BDHIQ derivatives were tested in vitro against L1210 leukemia cells. **II1**, **II21** and **II22** (IC_{50} 4.1, 2.5 and 1.4 μM, respectively) were the most potent to inhibit the proliferation of L1210 cells. Furthermore, these α-keto-imines BDHIQ induced an accumulation of L1210 cells in the G1 phase of the cell cycle.[8]

In conclusion, we have prepared a series of α-keto-imines BDHIQ's by a simple and efficient method which can be applied for the synthesis of new antitumoral agents.



Scheme 2. *Reagents and conditions*: (i) $PhCH_2Cl$, K_2CO_3, EtOH, refluxed 5 h; (ii) CH_3NO_2, NH_4OAc, AcOH, refluxed 4 h; (iii) THF, $LiAlH_4$, Et_2O, N_2 atm, refluxed 2 h; (iv) CH_2Cl_2, 5% aq. NaOH, 0°C, rt, 2 h; (v) $POCl_3$, dry CH_2Cl_2, refluxed 1.5 h; (vi) CH_3CN, 10% C/Pd, 5% aq. NH_4OH, 30 min.

References

1. Uff, B. C.; Kershaw, J. R.; Chhabra, S. R. *J. Chem. Soc., Perkin 1* **1972**, 479–483.
2. Leboeuf, M.; Ranaivo, A.; Cavé, A.; Moskowitz, H. *J. Nat. Prod.* **1989**, *52*, 516–521.
3. Wert, K. L.; Chackalamannil, S.; Miller, E.; Dalton, D. R.; Zacharias, D. E.; Glusker, J. P. *J. Org. Chem.* **1982**, *47*, 5141–5150.
4. Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. *J. Org. Chem.* **1999**, *64*, 6583–6596.
5. Blaskó, G.; Dörnyei, G.; Bárczai-Beke, M.; Péchy, P.; Szántay, C. *Heterocycles* **1983**, *20*, 273–278.
6. Kessar, S. V.; Mohammad, T.; Gupta, Y. P. *Indian J. Chem.* **1983**, *22B*, 321–324.
7. Chandrasekara, G. *Tetrahedron Lett.* **1995**, *36*, 1001–1002.
8. Cortes, D.; Cabedo, N.; Andreu, I.; Bermejo, A.; Atassi, G.; Pierre, A.; Caignard, D. H.; Renard, P. Nouveaux dérivés d'Isoquinoléines, leur procedé de préparation et les compositions pharmaceutiques qui les contiennent. Patent no. P2000/000185, 28.01.2001.
9. This controlled oxidation was previously performed on the preparation of enamines with an aporphine skeleton: Cava, M. P.; Edie, D. L.; Saá, J. M. *J. Org. Chem.* **1975**, *40*, 3601–3602.
10. Prepared by classic Bischler–Napieralski cyclodehydratation experiments.[11–14]
11. Cabedo, N.; Protais, P.; Cassels, B. K.; Cortes, D. *J. Nat. Prod.* **1998**, *61*, 709–712.
12. Andreu, I.; Cortes, D.; Protais, P.; Cassels, B. K.; Chagraoui, A.; Cabedo, N. *Bioorg. Med. Chem.* **2000**, *8*, 889–895.
13. Andreu, I.; Cabedo, N.; Tormo, J. R.; Bermejo, A.; Mello, R.; Cortes, D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1491–1494.
14. Cabedo, N; Andreu, I.; Ramírez de Arellano, M. C.; Chagraoui, A.; Serrano, A.; Bermejo, A.; Protais, P.; Cortes, D. *J. Med. Chem.* **2001**, *44*, 1794–1801.
15. General procedure for preparation of α-keto-imines BDHIQs: synthesis of 6-benzyloxy-7-methoxy-α-keto-3,4-benzyldihydroisoquinoline (**II1**). A solution of *N*-(3-benzyloxy-4-methoxyphenylethyl) phenylacetamide (500 mg, 1.33 mmol) in dry CH_2Cl_2 (10 mL) was treated with $POCl_3$ (0.5 mL, 5.4 mmol) and refluxed for 3 h. The reaction mixture was diluted with H_2O, made basic and extracted with CH_2Cl_2. The organic solution was washed with H_2O, dried and concentrated to give a brown oil. This residue was purified through 60 H silicagel column (CH_2Cl_2–MeOH 96:4) to afford the corresponding imine, **I1** (415 mg, 87%). **I1** (150 mg, 0.42 mmol) was treated with CH_3CN (70 mL) and 10% C/Pd (150 mg) and stirring for 1 h at room temperature. The reaction mixture was filtered over Celite and concentrated. The residue obtained was purified through 60 H silicagel column (hexane–EtOAc 60:40) to yield 6-benzyloxy-7-methoxy-α-keto-3,4-benzyldihydroisoquinoline, **II1** (141 mg, 90%), and its salt was prepared from 5% HCl in MeOH. $C_{24}H_{21}NO_3$; ^{1}H NMR* (400 MHz, $CDCl_3$) δ 8.03 (dd, $J=7.0$, 1.7 Hz, 2H, H-2′,6′), δ 7.59 (tt, $J=7.0$, 1.7 Hz, 1H, H-4′), δ 7.45 (t, $J=7.0$ Hz, 2H, H-3′,5′), δ 7.50–7.30 (m, 5H, OCH_2*Ph*-6), δ 6.97 (s, 1H, H-5), δ 6.77 (s, 1H, H-8), δ 5.21 (s, 2H, OCH_2Ph-6), δ 3.90 (t, $J=7.8$ Hz, 2H, CH_2-3), δ 3.78 (s, 3H, OCH_3-7), δ 2.75 (t, $J=7.8$ Hz, 2H, CH_2-4); ^{13}C NMR* (100 MHz, $CDCl_3$) δ 193.9 (C-α), δ 164.3 (C-1), δ 150.9 (C-6), δ 148.2 (C-7), δ 136.4 and 135.5 (C-1′ and C-1″), δ 133.8 (CH-4′), δ 130.9 (C-4a), δ 130.4 (CH-2′,6′), δ 130.3 (CH-3′,5′), δ 128.6–127.2 (OCH_2*Ph*-6), δ 119.6 (C-8a), δ 112.7 (CH-8), δ 110.2 (CH-5), δ 70.8 (OCH_2Ph-6), δ 56.2 (OCH_3-7), δ 42.2 (CH_2-3), δ 25.3 (CH_2-4); EIMS m/z (%) 371 $[M]^+$ (36), 280 (61), 266 (4), 105 (25), 91 (100), 77 (27). *The assignments were made by COSY 45, DEPT and HMQC.
16. The imines BDHIQ (compounds **I**) showed characteristic benzylic methylene signals at about 4.1 and 43 ppm in ^{1}H and ^{13}C NMR, respectively.