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BERBIN-8-ONES FROM 2'-HALOGENO-1-BENZYLISOQUINOLINES AND METAL CARBONYLS

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Summary: The title compounds were synthesised from 2'-halogeno-1-benzylisoquinolines, their 3,4-dihydro- or 1,2,3,4-tetrahydro-derivatives and metal carbonyls under mild conditions.

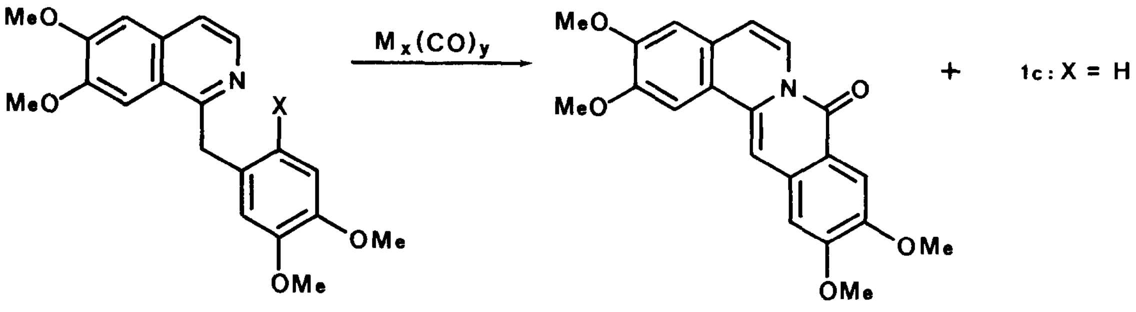
Several ways of preparing berbin-8-ones are known,[1] the most practical being the Vilsmeier - Haack cyclisation of papaverine or 3,4-dihydropapaverine and subsequent hydrolysis of the intermediate salt.[2] Another convenient route is the one developed by Pictet.[3] Recently was reported the synthesis of a tetrahydroberbin-8-one via azacarbonylative cyclisation catalysed by Pd^{II}.[4] The hitherto used approaches, however, require basic or acidic often forcing reaction conditions.

Several examples are known of dehalogenation by means of iron carbonyls.[5a,b] In all cases, however, the halogen is activated by neighbouring carbonyl group or is benzylic. The only example of carbonylative dehalogenation of aryl halide is the conversion of PhI into benzophenone via triiron dodecacarbonyl.[5a]

We wish to report a simple and convenient synthesis of berbin-8-ones based on the use of readily accessible starting materials, the relatively cheap $Fe_3(CO)_{12}$ and mild reaction conditions.[6]

The results of the reaction of 2'-halogenopapaverines 1a[7] and 1b[8] with various transition metal carbonyls are given in the Scheme. In all cases the berbin-8-one 2 was accompanied by the dehalogenation product 1c. The di- and tetrahydroisoquinolines 3a and 5 were also cyclised to berbin-8-ones 4 and 6, respectively.[9]

Under the presently used conditions the 1-phenyl-tetrahydroisoquinoline derivative 7[10] was shown not to cyclise to the 5-membered lactam. Instead, only debromination was observed, leading to 8 (38%).[11] The same result was obtained after addition of a catalytic amount of $CoCl_2.6H_2O$.[12] The 3,4-dihydroisoquinoline 9[13] was obtained on oxidation of 7 with DDQ at room temperature. Its treatment with $Fe_3(CO)_{12}$ gave a complex intractable mixture.



1

2

	$M_x(CO)_y$	2 (%)	1c (%)
1a: X = Br	$Fe_3(CO)_{12}$	43	34
	$Fe_2(CO)_9$	6	62[a]
	$Fe(CO)_5$	-[b]	-[b]
	$Co_2(CO)_8$	73	-[c]
	$Ru_3(CO)_{12}$	-[d]	-[d]
	$Mn_2(CO)_{10}$	-[b]	-[b]
1b: X = I	$Fe_3(CO)_{12}$	60	20

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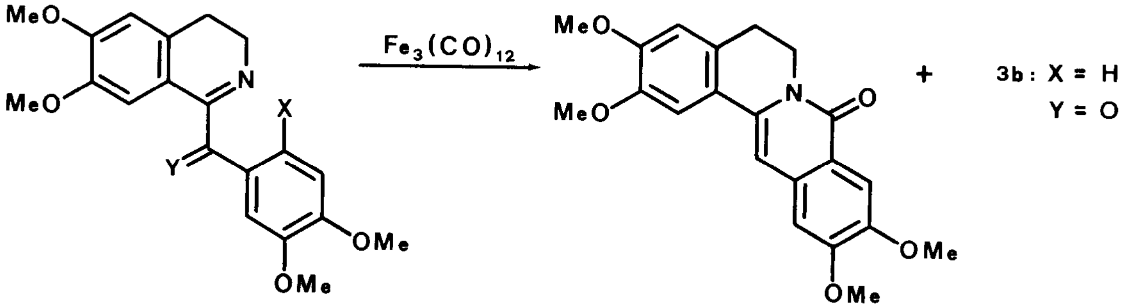
[a] determined by means of ^1H NMR in a mixture with unreacted 1a (25%); [b] no reaction at room temperature; only traces detected after refluxing in DME for 7 h; [c] traces detected by TLC but not isolated; [d] no reaction at room temperature and at reflux in DME.

The model compound 10[14] was recovered unchanged after treatment with $Fe_3(CO)_{12}$ in DME for several days indicating in this manner the importance of nitrogen in these reactions. The absence of dehalogenation illustrates the necessity of intramolecular complexation with the metal carbonyl in order to effect this reaction.

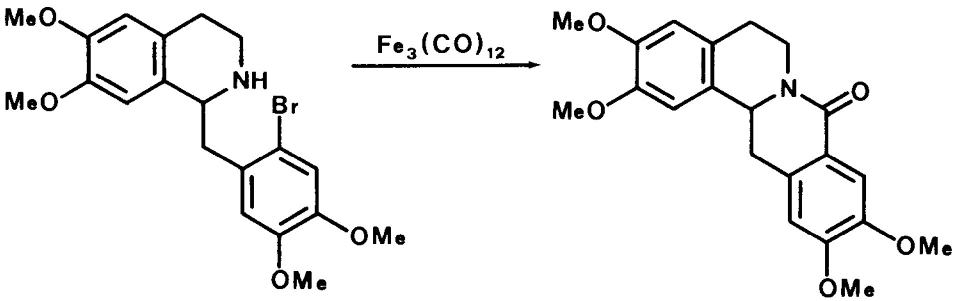
On the other hand a red iron complex more polar than papaverine was chromatographically detected in the reaction of papaverine with $Fe_3(CO)_{12}$. This complex was similar to the complexes observed by the cyclisation of 1a, 1b, 3a and 5 when using the same iron carbonyl with respect to polarity, colour, rate of formation and stability. The papaverine complex, however, did not produce the berbin-8-one 2. The presence of a halogenated in 2'-position aromatic ring appears therefore necessary for activation of the carbonylation reaction.[16]



3a : X = Br, Y = 2H

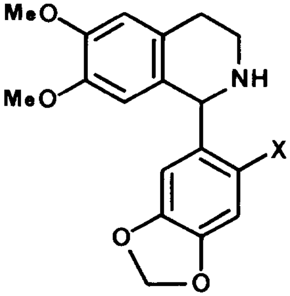
4 22%

19%



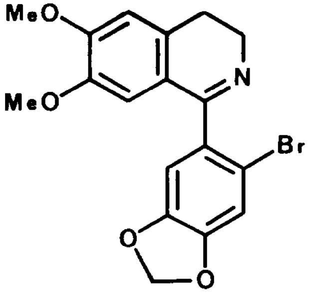
5

6 53%



7 : X = Br

8 : X = H



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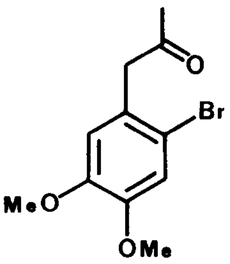

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References and Notes

1. M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research" - 1972-1977, Plenum Press, New York & London, 1978.
2. N. T. Le Quang Thuan and J. Gardent, C. r. Acad. Sci. Ser. C, 270, 835 (1970).
3. A. Pictet and A. Gams, Chem. Ber. 44, 2480 (1911).
4. G. D. Pandey and K. P. Tiwari, Synth. Commun. 9, 895 (1979).
5. "Comprehensive Organometallic Chemistry", Ed. Sir G. Wilkinson, Pergamon Press, 1982, a) vol. 8, p.159; b) vol. 4, pp. 251, 333, 430, 448 and 571.
6. In a typical procedure 1a (1 mmol) was treated with $Fe_3(CO)_{12}$ (2 mmol) in dry DME under argon at r.t. for 8 h. Filtration through a short silica gel column, evaporation to dryness, addition of 5% HCl and extraction with toluene afforded 2. Basification of the aqueous layer, extraction with ether and recrystallisation from ethanol gave 1c.
7. O. Anderson, Ann., 94, 238 (1854).
8. L. S. Trifonov and A. S. Orahovats, Commun. of the Department of Chemistry, Bulg. Acad. Sci., 11(2), 297 (1977).
9. Compounds 1c, 2 and 3b were directly compared with authentic samples, while compounds 4 and 6 were unambiguously converted to 2 and 4, respectively, by known procedures.[2,15]
10. Mp 109.0-112.5°C (EtOH); IR ($CHCl_3$): 3450 m, sh, 3300 m, br, 1595 m; ^1H NMR (250 MHz, $CDCl_3$): 7.06 (s, 1H, H-C(3')), 6.70 (s, 1H, H-C(6')), 6.46 (s, 1H, H-C(5)), 6.28 (s, 1H, H-C(8)), 5.96 and 5.94 (AB q, 2H, J = 1,2 Hz, OCH_2O), 5.44 (s, 1H, H-C(1)), 3.89 and 3.71 (each s, 3H, 2 x CH_3) 3.2-3.0 (m, 2H, $H_2C(3)$), 3.00-2.75 (m, 2H, $H_2C(4)$), 1.80 (br. s, 1H, NH); MS (70 eV): 393 (25), 392 (M^+, 25), 391 (25), 390 (M^+, 23), 378 (5), 376 (6), 192 ($M-C_7H_4Br$, 100).
11. T. Kametani, H. Sugi and S. Shibuya, Tetrahedron, 27(12), 2409 (1971).
12. M. O. Albers, N. J. Coville, T. V. Ashworth, E. Singleton and H. E. Swanepoel, J. Chem. Soc., Chem. Comm., 1980, 489.
13. Mp 150.0-152.5°C (MeOH); IR ($CHCl_3$): 3420 m, sh, 3300 m, br, 1570 s; ^1H NMR (250 MHz, $CDCl_3$): 7.03, 6.90, 6.75 and 6.49 (each s, 1H, aromatic), 6.06 and 6.03 (each s, 1H, OCH_2O), 4.1-3.9 (m, 2H, $H_2C(3)$), 3.95 and 3.75 (each s, 3H, OCH_3), 2.9-2.6 (m, 2H, $H_2C(4)$); MS (70 eV): 392 (8), (8), 391 (M^+, 33), 390 (15), 389 (M^+, 33), 311 (18), 310 (M^+-Br, 100).
14. E. V. Kuznetsov, I. V. Shcherbakova, V. I. Ushakov and G. N. Dorofeenko, Zh. Org. Khim., 13(3), 631 (1977).
15. G. R. Lenz, J. Org. Chim. 39(19), 2846 (1974).
16. G. L. Geoffroy and M. S. Wrighton, "Organometallic Photochemistry", Academic Press, 1979, p. 2.

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