Pergamon

Tetrahedron Letters, Vol. 36, No. 37, pp. 6669-6672, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01274-5

Synthesis of New 4-Alkylamino-5-methoxy-*2H*-pyran-2-ones

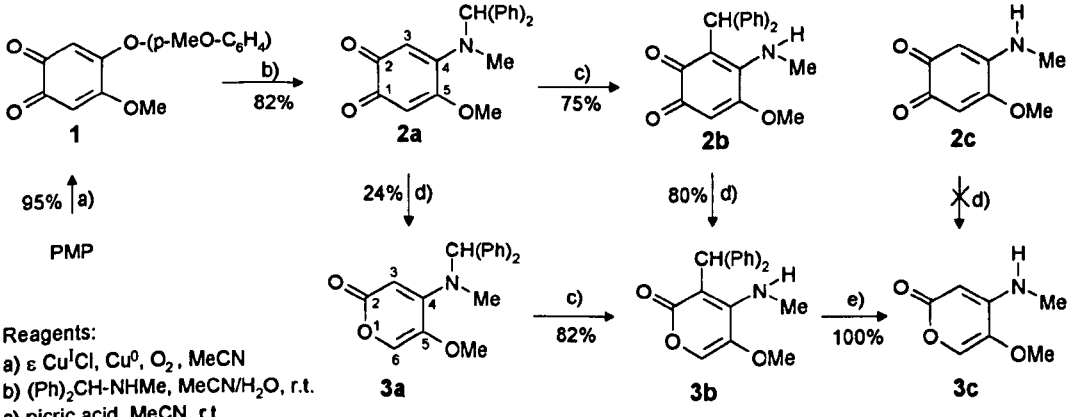
Loïk Viallon †, Olivia Reinaud, Patrice Capdevielle and Michel Maumy

Laboratoire de Recherches Organiques de l'ESPCI, associé au CNRS,
10 rue Vauquelin, 75231 Paris Cedex 05, France.

Abstract: 4-alkylamino-5-methoxy-1,2-benzoquinones **2a, b** *are selectively oxidized by magnesium monoperoxyphtalate (MMPP) into new 4-alkylamino-5-methoxy-2H-pyran-2-ones* **3a, b**. *The acid-catalyzed migration of a benzhydryl group* (**3a** → **3b**) *as well as its quantitative C-dealkylation* (**3b** → **3c**) *are described. All three reactions are original, proceed with high yields, thus providing an efficient pathway to obtain new and highly substituted pyranonic structures.*

We have recently described an easy pathway to synthetize a large variety of new amino-1,2-benzoquinones within two steps (Scheme 1, a and b) starting from para-methoxyphenol (PMP)[1]. Since the compounds were readily accessible, we sought to take advantage of their highly functionalized dissymetric structure and transform them into new molecules otherwise difficult to obtain with the classical tools of the organic chemist.

This strategy led us to discover an efficient route to original 2*H*-pyran-2-ones which are selectively substituted in 3-, 4- and 5- positions.



Scheme 1

† Deceased January 1994

N-Methyl-N-benzhydrylamino- methoxy-1,2-benzoquinone **2a** is issued (Scheme 1, b) from the selective nucleophilic displacement[1] of the *p*-methoxyphenoxy group of 1,2-benzoquinone **1** by N-methyl benzhydrylamine in a $MeCN/H_2O$ (80/20) mixture.[2] This alkylamino-1,2-benzoquinone **2a** can undergo a facile acid-catalyzed rearrangement toward formation of its C_3-alkylated isomer **2b** with a good yield (Scheme 1, c).[3]

When magnesium monoperoxyphtalate (MMPP) was added at room temperature to a methanolic solution of either aminoquinone **2a** or **2b** containing aqueous 1M $KHCO_3$ (in order to maintain a slightly basic pH), the reaction mixture underwent a fast decoloration attesting to the disappearance of the quinonic moieties.[4] After overnight reaction with 1.4 eq. of MMPP (i.e. 2.8 eq. of peracid), 2*H*- pyran-2-ones **3a** [5] and **3b** [6] were isolated with a 24% and 82% yield respectively.

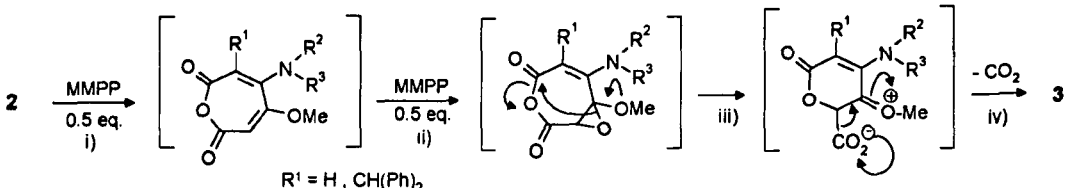
The structures of compounds **3** were determined by comparative ^1H NMR: each of H-3 and H-6 protons of the pyranone ring of compounds **3a,c** have similar shifts (respectively 5 and 7 ppm). The sole proton present on **3b** ring is observed at 7 ppm, which allows us to assign it as H-6 and not as H-3. Therefore the regioisomeric structures 5-alkylamino-4-methoxy-2*H*-pyran-2-one can be excluded in all cases.

A t.l.c. monitoring of the reaction revealed that the transposition was complete on the condition that more than 1 eq. of MMPP was added (> 2 eq. of peracid). When $KHCO_3$ was omitted from the reaction mixture, yields in products **3** were considerably diminished (< 10%).

The reaction is believed to proceed in 4 steps:

i) a Baeyer-Villiger type oxidation, well known in *ortho*quinone series[7-10], transforms the starting amino-1,2-benzoquinones into a cyclic polyunsaturated anhydride (*cis-cis* muconic structure) (Scheme 2). The reactivity of its double bonds towards an electrophilic oxidant is higher than those of the quinonic precursor due to its more electron-rich[11] and less aromatic character.

ii) As a consequence, the anhydride intermediate is not isolated but undergoes a second oxidation by the peracid thus producing an epoxidized intermediate. The selectivity of the epoxidation process is largely directed by the relative steric hindrance of the two double bonds: the highest yield in pyranone is obtained when the bulky group substitutes the 3,4- double bond itself thus protecting it from the epoxidation process; 4-methylamino-5-methoxy-1,2-benzoquinone **2c** ($R^{1,2}$ = H, R^3 = Me) does not give rise to any isolable pyranone but to a mixture of unidentified colorless products.



Scheme 2

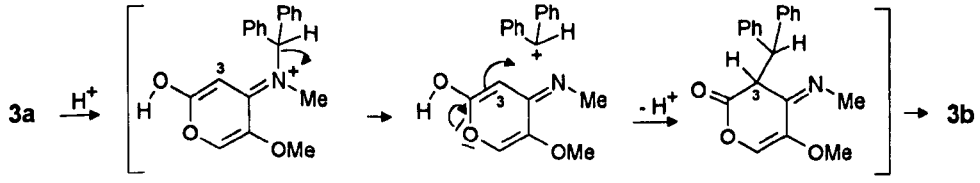
iii) The opening of the epoxide ring, promoted by the nucleophilic assistance of the methoxy group, gives rise to a S_Ni type attack on carbonyl-2 toward formation of a new pyranic structure.

iv) Finally, decarboxylation of the latter yields pyranic compounds **3**.

With the exception of the previously reported ruthenium-[12] or vanadium-[13,14] catalyzed oxygenations of 3,5-di-*tert*-butylcatechol into a mixture of di-*tert*-butylmuconic anhydride and 4,6-di-*tert*-butyl-2*H*-pyrone, this is the first example of such a reaction sequence. The authors proposed an oxygen insertion on 3-position of transiently formed 3,5-di-*tert*-butyl-benzoquinone followed by decarbonylation. Such a mechanism is, in our case, unconsistent with the observed regiochemistry and the necessary requirement of 2 molar equivalents of peracidic oxidant for the reaction to reach completion.

It is of some importance to emphasize the high efficiency of the reaction in case **b** where the benzhydryl substituent plays the role of protecting group. Indeed, the latter can be easily and quantitatively removed by simple heating at 70°C, for 30 mn, in concentrated sulfuric acid [15] (**3b** → **3c**).

On the other hand, in presence of a catalytic amount of picric acid in dry MeCN, pyranone **3a** undergoes the regioselective migration of its benzhydryl group on carbon 3 position, toward formation of pyranone **3b** with 82% yield.[16] Such a rearrangement was previously described by us on 1,2-benzoquinonic structures [3,17] (for example **2a** → **2b**) and shown to be ineffective on a simple enaminone.[3] Hence, rearrangement of pyranone **3a** provides a second example of this original process whose mechanism, similar to the one we proposed in the benzoquinonic series, is depicted in Scheme 3:



Scheme 3

The oxygen atom of the heterocycle increases the basicity of the system compared to 3(N-methyl-benzhydrylamino)-2-cyclohexenone [3] and thus favors both protonation of the carbonyl and trapping of transient benzhydryl cation by the nucleophilic C-3 .

In conclusion, we have described here a new reaction within the oxidative transformation of a quinone into a dihydropyranone. A high yield is obtained thanks to the use of a protecting group for one of the double bonds of the conjugated system. Thus, starting from PMP, the whole sequence of reaction provides an efficient pathway for new pyranones with a 47% overall yield.

REFERENCES AND NOTES

1. Viallon, L.; Reinaud, O.; Capdevielle, P.; Maumy, M. *Synthesis* **1995**, in press.
2. Reinaud, O.; Capdevielle, P.; Maumy, M. *Synthesis* **1987**, 790-794.
3. Viallon, L.; Reinaud, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1995**, in press.
4. To a stirred solution of pure quinone **2a** (mp = 196°C) (1.0 g, 3 mmol) in MeOH (30 ml) and 1M aqueous $KHCO_3$ (15 ml), MMPP (2.5 g, 4.2 mmol) was added within 2 h. After 24 h at room temperature, MeOH was distilled under vacuum and the organic layer extracted with ether (100 ml) and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel with a mixture of cyclohexane and ethyl acetate (40/60) as an eluent to yield pyranone **3a** (0.791 g, 2.46 mmol, 82%).
5. **3a**, colorless crystals, mp = 138°C, Analysis. Found %: C, 74.62; H, 5.98; N, 4.39; Calc.% for $C_{20}H_{19}NO_3$: C, 74.75 ; H, 5.96 ; N, 4.36; ^1H NMR ($CDCl_3$ / TMS) δ: 2.65 (s, 3H, N-Me); 3.55 (s, 3H, -OMe); 5.25 (s, 1H, O=C-C<u>H</u>=C-N); 6.65 (s, 1H, N-CH-); 7.05 (s, 1H, O-C<u>H</u>=C-OMe); 7.1 - 7.5 (m, 10 H, 2 Ph). IR (KBr), ν (cm^{-1}) : 1702, 1668, 1632.
6. **3b**, colorless crystals, mp = 176°C, Analysis: Found %: C, 74.69; H, 5.94; N, 4.40; Calc.% for $C_{20}H_{19}NO_3$: C, 74.75 ; H, 5.96 ; N, 4.36 , ^1H NMR ($CDCl_3$ / TMS) δ, *J* (Hz): 2.75 (d, *J* = 6, 3H, N-Me); 3.65 (s, 3 H, -OMe); 4.8 (s, exch. D_2O, 1H, N-H); 5.95 (s, 1H, -CH-); 7.0 (s, 1H, O-C<u>H</u>=C-OMe); 7.2 - 7.4 (m, 10 H, 2 Ph). IR (KBr), ν (cm^{-1}) : 1669, 1650.
7. Böeseken, J.; Sloof, G. *Recueil Tr. Ch. Pays-Bas* **1930**, *49*, 91-94.
8. Karrer, P.; Schwyzer, R ; Neuwirth, A. *Helvetica* **1948**, *31*,1210-1214.
9. Brassard, P.; Karrer, P. *Helvetica* **1960**, *43*, 262-264.
10. Hewgill, F R.; Lee, S.L. *J. Chem. Soc., C* **1969**, 2080-2086.
11. Stevens C.L.; Tazuma J. *J. Am. Chem. Soc.* **1954**, *76*, 715-717.
12. Matsumoto, M.; Kuroda, K. *J. Am. Chem. Soc.* **1982**, *104*, 1433-1434.
13. Tatsuno, Y.; Tatsuda, M.; Otsuka, S. *J. Chem. Soc. Chem. Comm.* **1982**, 1100-1101.
14. Tatsuno, Y.; Nakamura, C.; Saito, T. in « The Role of Oxygen in Chemistry and Biochemistry », Ando, W. and Moro-Oka, Y., Eds., Elsevier, 1988 pp. 321-324.
15. A solution of pyranone **3b** (0.450g, 1.4 mmol) in concentrated (95%) sulfuric acid (5 ml) was heated at 70°C for 30 mn. Ice (50 g) was slowly added to the cooled solution. Pure pyranone **3c**[15] was extracted with dichloromethane (30 ml), and isolated as colorless crystals, mp = 132°C, Analysis: Found %: C, 54.22; H, 5.83, N, 8.99; Calc.% for $C_7H_9NO_3$: C, 54.19 ; H, 5.85 ; N, 9.03; ^1H NMR ($CDCl_3$ / TMS) δ, *J* (Hz)· 2.85 (d, *J* = 6, 3H, N-Me); 3.7 (s, 3H, -OMe); 5.1 (s, 1 H, O=C-CH=C-N); 5.3 (s exch. D_2O, 1H, N-H); 6.9 (s, 1H, O-CH=C-OMe) IR (KBr), ν (cm^{-1}) : 1675, 1651, 1620.
16. Pyranone **3a** (1.61 g, 5 mmol) and picric acid (0.23g, 1 mmol) are dissolved at room temperature in anhydrous acetonitrile (5 ml). **3a** completely reacted within 2 h (monitored by tlc). The solvent was evaporated under reduced pressure, the residue dissolved in dichloromethane (30 ml), washed with aqueous 1M K_2CO_3 (10 ml), dried over $MgSO_4$. Purification by column chromatography on silica gel using cyclohexane / ethyl acetate (50:50, v/v) as an eluent provided 1.32 g (82%) of pyranone **3b**.
17. Reinaud, O.; Capdevielle, P.; Maumy, M. *Synthesis* **1987**, 4167-4176.

(*Received in France* 22 *May* 1995; *accepted* 6 *July* 1995)