A GENERAL FORMATION OF QUINONE IMINES AND QUINONE IMINE ACETALS: AN EFFICIENT SYNTHESIS OF 5-OXYGENATED INDOLES†

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Abstract - A general and high-yield synthesis of benzoquinone imines and benzoquinone imine monoacetals leading to 5-oxygenated indoles was developed.

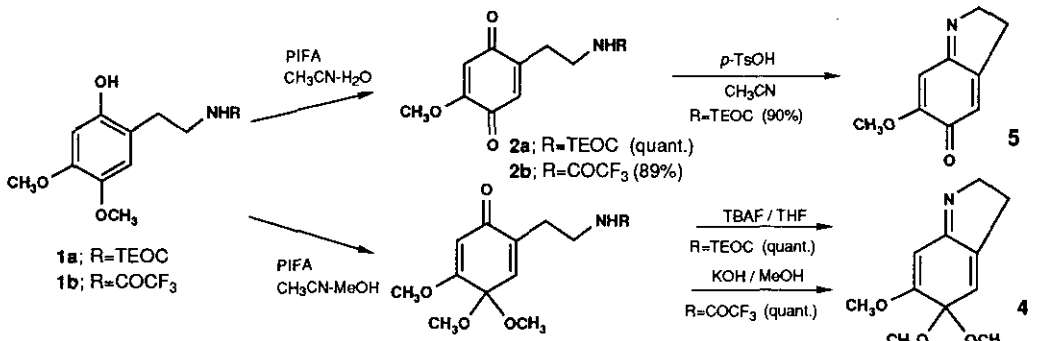
Quinone imines and quinone imine monoacetals have been proposed as intermediates in a number of biological processes[1] and the former moieties were involved in the recently isolated marine alkaloids, amphimedine,[2] cystodytin,[3] diplamine,[4] isobatzellines,[5] wakayin,[6] ascididemin,[7] and discorhabdins.[8] Because of unstability of these imines under the conditions used for their formation, only a few preparative methods have been reported by anodic oxidation of anilides[9] or 4-methoxyphenol derivatives[10] or by hypervalent iodine oxidation of aniline derivatives.[11] We now report an intramolecular imine formation from benzoquinones and benzoquinone monoacetals bearing a 2-aminoethyl side chain, which provides an efficient route to 5-oxygenated indoles.

The starting quinones (**2**) and quinone monoacetals (**3**) were readily prepared from

†This paper is dedicated to Dr. Masatomo Hamana on the occasion of his 75th birthday.

the protected 2-aminoethyl-4-methoxyphenols (**1**) by our hypervalent iodine-oxidation method.[12,13] Oxidation of the aminoethylphenol (**1a**) protected by trimethylsilylethoxycarbonyl (TEOC) group with equimolar amount of phenyliodine bis(trifluoroacetate) (PIFA)[14] in acetonitrile (CH_3CN)-water at room temperature for 10 min gave the benzoquinone (**2a**) and in CH_3CN-methanol under the same conditions gave the benzoquinone monoacetal (**3a**), respectively in high yields. Other starting compounds (**2b-d** and **3b,c**) were prepared from the corresponding 4-methoxyphenols in high yields.

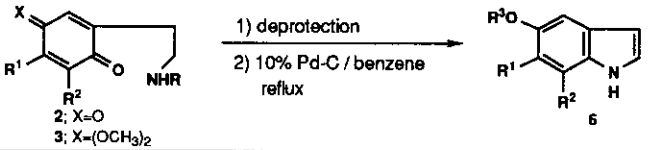
The imine formation from the quinone monoacetal (**3**) was smoothly performed by deprotection of the amino group to give a quantitative yield of the quinone imine monoacetal. Thus, to a solution of **3a** in tetrahydrofuran (THF) was added a solution of 2.0 equiv. of *n*-tetrabutylammonium fluoride (TBAF) in THF and the mixture was stirred at room temperature for 3 h to give **4**.[15] Treatment of **3b** with KOH in methanol under the same conditions also gave **4**. On the other hand, the imine formation from the benozoquinone (**2**) was quite troublesome. After many unsuccessful trials under the conditions using TBAF in THF, HCl-methanol, KOH-methanol, $TiCl_4$-CH_2Cl_2 in the presence of molecular sieves 3A, only the treatment of the TEOC-protected **2** with anhydrous *p*-toluenesulfonic acid (*p*-TsOH) gave the desired benzoquinone imine. Thus, treatment of **2a** with *p*-TsOH in CH_3CN at room temperature for 3 h gave **5**[15] in 90% yield.

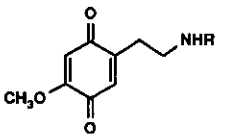
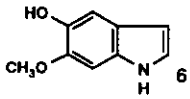
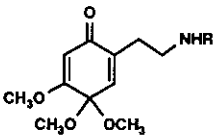
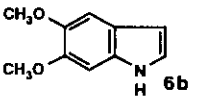
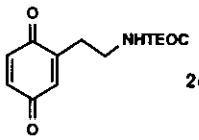
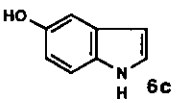
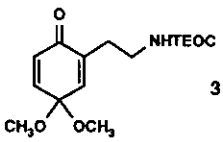
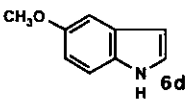
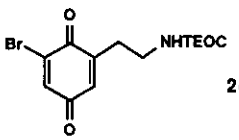
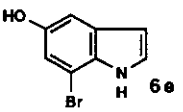


Scheme I

These methods are quite useful for the formation of benzoquinone imines and their acetals, which were spontaneously converted to the corresponding 5-oxygenated indoles (**6a-e**) by the treatment with 10% Pd-C in refluxing benzene for 3 h. The results are summarized in Table I.

Table I
Preparation of 5-Oxygenated Indoles (**6a-e**) via Quinone Imines and Quinone Imine Monoacetals



Run	Starting Materials		Reaction Conditions	Products[a]	Yields (%)[b]
1		**2a**; R=TEOC	1) *p*-TsOH / CH_3CN 2) 10%Pd-C / reflux	 **6a**	90
2		**2b**; R=$COCF_3$	KOH / MeOH		—[c]
3		**3a**; R=TEOC	1) TBAF / THF / r.t. 2) 10%Pd-C / reflux	 **6b**	quant.
4		**3b**; R=$COCF_3$	1) KOH / MeOH / r.t. 2) 10%Pd-C / reflux		quant.
5		**2c**	1) *p*-TsOH / CH_3CN 2) 10%Pd-C / reflux	 **6c**	65
6		**3c**	1) TBAF / THF / r.t. 2) 10%Pd-C / reflux	 **6d**	quant.
7		**2d**	1) *p*-TsOH / CH_3CN 2) 10%Pd-C / reflux	 **6e**	95

a) All satisfactory spectral and analytical data were obtained.
b) Overall yields were shown from the starting quinones (**2**) or quinone acetals (**3**).
c) Complex mixture was obtained.

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15. **4**: Ir ($CHCl_3$) 1620 and 1580 cm^{-1} ; ^1H nmr ($CDCl_3$) δ 2.72 (2H, m, $C\underline{H}_2CH_2N{=}C$), 3.25 (6H, s, $OCH_3\times 2$), 3.82 (3H, s, OCH_3), 4.12 (2H, t, J=6 Hz, $C\underline{H}_2N{=}C$), 5.87 (s, 1H, 7-CH), 6.04 (s, 1H, 4-CH); high resolution ms calcd for $C_{11}H_{15}NO_3$ (M^+) 209.1052, found 209.1058.

5: Ir ($CHCl_3$) 1645, 1615, 1510 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.91 (2H, dt, J=2, 4 Hz, $C\underline{H}_2CH_2N{=}C$), 3.86 (3H, s, OCH_3), 4.34 (2H, t, J=4 Hz, $C\underline{H}_2N{=}C$), 6.45-6.50 (1H, m, 4-CH), 6.56 (1H, s, 7-CH); high resolution ms calcd for $C_9H_9NO_2$ (M^+) 163.0633, found 163.0634.

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