

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

Yasuyuki Kita,* Hirofumi Tohma, Masanao Inagaki, and Kenji
Hatanaka

Faculty of Pharmaceutical Sciences, Osaka University,
1-6, Yamada-oka, Suita, Osaka 565, Japan

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

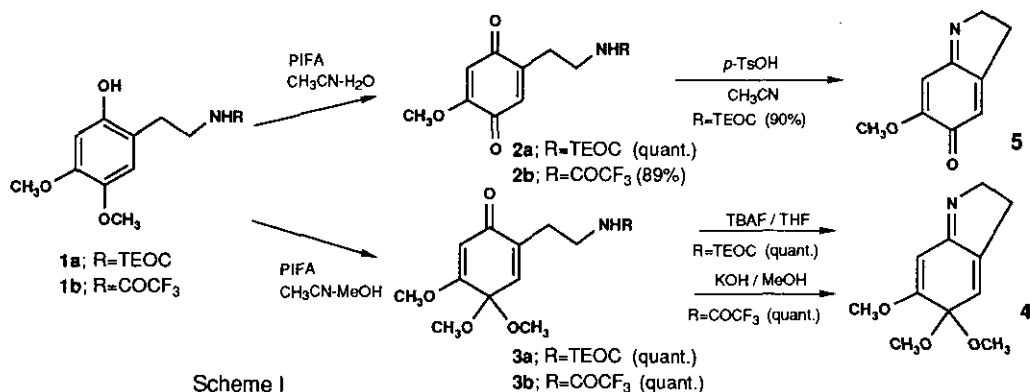
Quinone imines and quinone imine monoacetals have been proposed as intermediates in a number of biological processes¹ and the former moieties were involved in the recently isolated marine alkaloids, amphimedine,² cystodytin,³ diplamine,⁴ isobatzellines,⁵ wakayin,⁶ ascididemin,⁷ and discorhabdins.⁸ Because of unstability of these imines under the conditions used for their formation, only a few preparative methods have been reported by anodic oxidation of anilides⁹ or 4-methoxyphenol derivatives¹⁰ 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 (CH₃CN)-water at room temperature for 10 min gave the benzoquinone (**2a**) and in CH₃CN-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 benzoquinone (**2**) was quite troublesome. After many unsuccessful trials under the conditions using TBAF in THF, HCl-methanol, KOH-methanol, TiCl₄-CH₂Cl₂ 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 CH₃CN at room temperature for 3 h gave **5**¹⁵ in 90% yield.



Scheme 1

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) deprotection 2) 10% Pd-C / benzene reflux 2; X=O 3; X=(OCH₃)₂ 6				
1		1) <i>p</i> -TsOH / CH ₃ CN 2) 10%Pd-C / reflux		90
2		KOH / MeOH		— ^{c)}
3		1) TBAF / THF / r.t. 2) 10%Pd-C / reflux		quant.
4		1) KOH / MeOH / r.t. 2) 10%Pd-C / reflux		quant.
5		1) <i>p</i> -TsOH / CH ₃ CN 2) 10%Pd-C / reflux		65
6		1) TBAF / THF / r.t. 2) 10%Pd-C / reflux		quant.
7		1) <i>p</i> -TsOH / CH ₃ CN 2) 10%Pd-C / reflux		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 (CHCl₃) 1620 and 1580 cm⁻¹; ¹H nmr (CDCl₃) δ 2.72 (2H, m, CH₂CH₂N=C), 3.25 (6H, s, OCH₃ × 2), 3.82 (3H, s, OCH₃), 4.12 (2H, t, J=6 Hz, CH₂N=C), 5.87 (s, 1H, 7-CH), 6.04 (s, 1H, 4-CH); high resolution ms calcd for C₁₁H₁₅NO₃ (M⁺) 209.1052, found 209.1058.
5: Ir (CHCl₃) 1645, 1615, 1510 cm⁻¹; ¹H nmr (CDCl₃) δ 2.91 (2H, dt, J=2, 4 Hz, CH₂CH₂N=C), 3.86 (3H, s, OCH₃), 4.34 (2H, t, J=4 Hz, CH₂N=C), 6.45-6.50 (1H, m, 4-CH), 6.56 (1H, s, 7-CH); high resolution ms calcd for C₉H₉NO₂ (M⁺) 163.0633, found 163.0634.

Received, 5th November, 1991