Pergamon

Tetrahedron Letters 43 (2002) 5295–5296

TETRAHEDRON
LETTERS

# Novel ring transformation of quinolines to indole derivatives in two steps

Michiharu Sugiura,* Natsuyo Yamaguchi, Takafumi Saya, Misato Ito, Koosuke Asai and Isamu Maeba

*Faculty of Pharmacy, Meijo University, Yagotoyama 150, Tempaku-ku, Nagoya 468-8503, Japan*

Received 28 January 2002; revised 30 May 2002; accepted 31 May 2002

---

**Abstract**—Dimethyl 1-methoxycarbonyl-1,2-dihydroquinoline-2-phosphonates **1a**–**f** obtained from corresponding quinoline derivatives **2** in one step were ozonized in $CHCl_3$ and $CH_3COOH$. Treatment of the resulting mixture with $NaHCO_3$ produced the 2-formyl-1-methoxycarbonylindole derivatives **5a**–**g** in high yields. The ring transformation of quinolines **2** to indoles **5** proceeded under mild conditions. © 2002 Elsevier Science Ltd. All rights reserved.

---

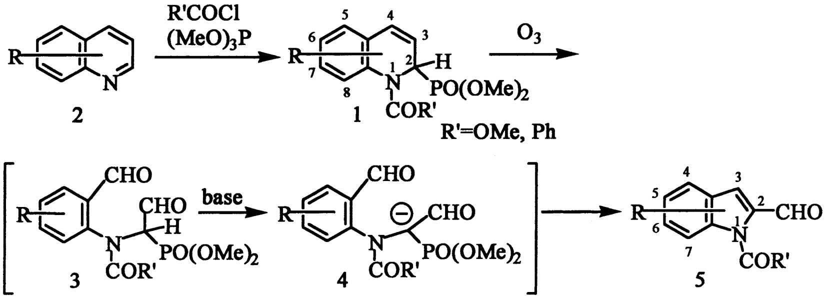
Considerable efforts have been made to synthesize indole moieties from commercially available starting materials in short steps. To date, there have been several procedures reported for the synthesis of indole such as the Fisher,[1] Bischler–Mohlau,[2] Martinet,[3] Madelung,[4] Nenitzescu,[5] Reissert,[6] Sandmeyer,[7] Stolle[8] and Fukuyama[9] methods. This report describes a novel method for the ring transformation of quinolines to indole derivatives in two steps producing a high yield.

The dimethyl 1-acyl-1,2-dihydroquinoline-2-phosphonates **1** obtained from quinoline **2a** in one step[10] have a double bond between the 3 and 4 positions. We predicted that compound **3** with two carbonyl groups would be produced by the reaction of **1** with ozone. In the structure of **3**, the phosphonate and carbonyl groups are substituted at the same C atom, so the anion compound **4** is readily obtained by treatment with a weak base for example $NaHCO_3$, and the indole derivative **7** can be obtained via an intramolecular Wittig–Horner reaction (Scheme 1).

The 1-methoxycarbonyl-2-phosphonates **1** were obtained by modifying the Akiba et al. method[10] (Table 1).

### Typical oxidation procedure:

Compound **1a**[10] (0.01 mol) was dissolved in $CHCl_3$ (500 ml) free from EtOH, then $CH_3COOH$ (5 ml) was added. Ozone was subsequently introduced into the



**Scheme 1.**

---

*Keywords*: pseudo base; phosphonate; dihydroquinoline; ozonation; formylindole.

* Corresponding author. Tel.: +81 52 832 1781; fax: +81 52 834 8780; e-mail: mitchy@ccmfs.meijo-u.ac.jp

PII: S0040-4039(02)01059-6

**Table 1.** Preparation of phosphonates **1** and formylindoles **5**

| **1** | R | Yield (%) | $^1$H NMR 2-, 3- and 4-H ($\delta$) | **5** | R | Yield (%) | $^1$H NMR 2-CHO and 3-H ($\delta$) |
|---|---|---|---|---|---|---|---|
| **a** | H | 85 | 5.64, 6.59, 6.05 | **a** | H | 99 | 10.42, 7.46 |
| **b** | 3-Me | 99 | 5.37, –, 6.35 | **b** | H[a] | 73 | 2.52,[b] 7.09 |
| **c** | 4-Me | 27 | 5.59, 5.86, – | **c** | 3-Me | 76 | 10.33, – |
| **d** | 6-Me | 88 | 5.65, 6.55, 6.03 | **d** | 5-Me | 95 | 10.40, 7.37 |
| **e** | 7-Me | 72 | 5.64, 6.56, 5.97 | **e** | 6-Me | 94 | 10.39, 7.45 |
| **f** | 6-MeO | 90 | 5.66, 6.56, 6.07 | **f** | 6-MeO | 98 | 10.43, 7.41 |
| | | | | **g** | H | 86[c] | 9.68, 7.47 |

[a] 2-Acetyl-1-methoxycarbonylindole.

[b] $COCH_3$.

[c] From dimethyl 1-benzoyl-1,2-dihydroquinoline-2-phosphonate.[10]

reaction mixture at room temperature. After the spot of **1a** disappeared on the TLC ($SiO_2/CH_2Cl_2$), the ozonized solution was washed several times with iced water to remove $CH_3COOH$. $NaHCO_3$ (0.02 mol) and water (50 ml) were added to the stirred $CHCl_3$ layer, and the entire mixture was kept at room temperature for 0.2 h. The $CHCl_3$ solution was separated and dried over $MgSO_4$, filtered, and concentrated. The residue was practically pure but purified where necessary by chromatographing on a silica gel column eluted with benzene to yield **5a** (Table 1).

Phosphonate **1** and indole **5** were each characterized by FAB-MS, IR, $^1$H, $^{13}$C, COSY, NOESY, CH-COSY and HMBC NMR analysis, and the spectroscopic data were in agreement with the reported structure.[11]

Although the COOMe group (**1a**) was compared with the PhCO group (dimethyl 1-benzoyl-1,2-dihydroquinoline-2-phosphonate[10]) at position **1**, there was no difference observed in the yields of **5a** and **5g**.

This novel method offers great potential in the synthesis of new medicines containing an indole moiety and can also be used for the synthesis of heat sensitive compounds due to the mild reaction conditions. The preparation of derivatives from many known biologically active substances for example, quinine, is possible using this novel reaction including the transformation of a quinoline moiety into an indole adduct.

## Acknowledgements

This work was partly supported by Ministry of Education, Culture, Sports, Science and Technology of Japan (High-Tech Research Center Project).

## References

1. (a) Ishii, H. *Acc. Chem. Res.* **1981**, *14*, 275–283; (b) Robinson, B. *Chem. Rev.* **1963**, *63*, 373–402; (c) Robinson, B. *Chem. Rev.* **1969**, *69*, 227–250.
2. (a) Bishler, A. *Chem. Ber.* **1892**, *25*, 2860–2879; (b) Bishler, A.; Fireman, P. *Chem. Ber.* **1893**, *26*, 1336–1349.
3. Sumpter, W. C. *Chem. Rev.* **1945**, *37*, 443–479.
4. Houlihan, W. J.; Uike, Y.; Parrino, V. A. *J. Org. Chem.* **1981**, *46*, 4515–4517.
5. Bernier, J. L.; Henichart, J. P. *J. Org. Chem.* **1981**, *46*, 4197–4198.
6. Cannon, J. G.; Demopoulos, B. J.; Long, J. P.; Flynn, J. R.; Sharabi, F. M. *J. Med. Chem.* **1981**, *24*, 238–240.
7. Marvel, C. S.; Hiers, G. S. *Org. Synth.* **1943**, Coll. Vol. I, 327–330.
8. Sumpter, W. C. *Chem. Rev.* **1944**, *34*, 393–434.
9. Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127–3128.
10. (a) Sugiura, M.; Asai, K.; Hamada, Y. *Heterocycles* **1996**, *43*, 953–958; (b) Akiba, K.; Negishi, Y.; Inamoto, N. *Synthesis* **1979**, 55–56.
11. For example **5a**: $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 10.42 (s, 2-CHO), 4.12 (s, $OCH_3$), 7.46 (s, 3-H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 183.87 (2-CHO), 151.81 ($\mathit{C}OOCH_3$), 137.65 (2-C), 117.12 (3-C), 54.34 ($COO\mathit{C}H_3$); IR (KBr): 1744, 1667 $cm^{-1}$; FAB-MS: $m/z$ 204 [$MH^+$].