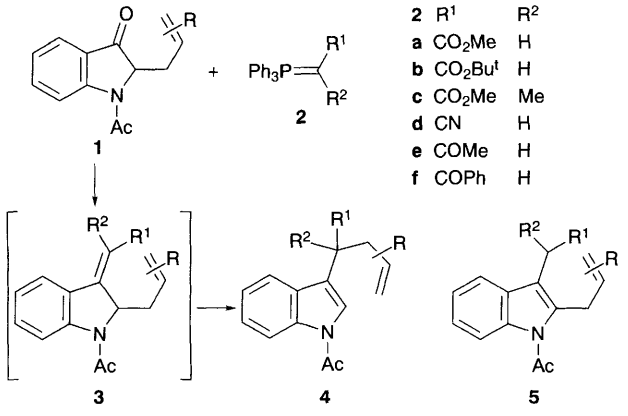
Tandem Wittig Reaction and Cope Rearrangement of 2-Allyl-1,2-dihydroindol-3-ones to 3-Indole Acetates

Tomomi Kawasaki, Kazuaki Watanabe, Kouhei Masuda and Masanori Sakamoto*

Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

Treatment of 2-allyl-1,2-dihydroindol-3-ones **1** with phosphonium ylides **2** in refluxing toluene gives 3-indole acetates **4** in good yields by tandem Wittig reaction and aromatization induced Cope rearrangement.

The Cope rearrangement has found substantial utility in the methodology of synthetic organic chemistry.[1] The rearrangement of unsubstituted hexa-1,5-diene is reversible to form preferentially highly substituted olefins in an equilibrium mixture. In order to completely shift the equilibrium in the desired direction, the reaction has exploited driving forces such as conjugation,[2,3] strain[4] or irreversible conversion[5] of one diene to a more stable product. However, there has been little use of aromatization[6] (*i.e.* the incorporation of a double bond of hexa-1,5-diene into an aromatic ring) to effect the Cope rearrangement, because of the difficulty of constructing the starting hexa-1,5-diene system. We here describe tandem Wittig olefination and aromatization induced Cope rearrangement of indolin-3-ones, which provides a new method for the synthesis of biologically interesting 3-indole acetic acid derivatives.[7]



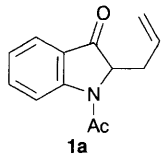
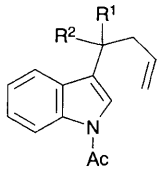
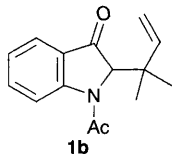
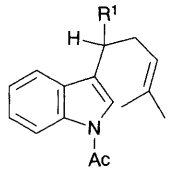
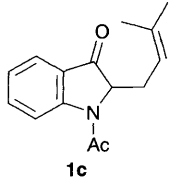
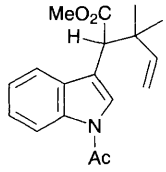
Scheme 1

The starting 2-allyl-1,2-dihydroindol-3-ones **1–c** were readily available by our previously described methods.[8] When the allylindol-3-one **1a** was treated with the phosphonium ylide **2a** in refluxing toluene for 5 h, the Wittig olefination followed by the Cope rearrangement of an intermediary 3-alkylidene-1,2-dihydroindole **3a** occurred smoothly to give 2-(indol-3-yl)pent-4-enoate **4a**† in 87% yield. Similar reaction of indol-3-ones **1a–c** with ylides **2a–f** afforded the corresponding 3-indole derivatives **4b–g** in good yields‡ (Table 1).

As can be seen from Table 1, either the bulkiness of the substituents in the ylide **2c** (entries 1 *vs.* 3) and 1,1-dimethylallyl group in the indol-3-one **1b** (entries 1 *vs.* 5) or the nucleophilicities[9] of the ylides (**2a, e, f**) (entries 5–7) affected the reaction, especially the initial Wittig reaction step. In the case of **1c**, the initial Wittig reaction proceeded smoothly, but the Cope rearrangement was slower due to the bulkiness of the 3,3-dimethylallyl group of **1c**. In all the cases examined, the Cope rearrangement of 1,5-diene **3** caused both aromatization and deconjugation of the olefins with ester, keto or cyano groups. This indicates the superiority of aromatization over conjugation as the well-known driving force in Cope rearrangement. Although it was found in our previous work[10] that the Wittig reaction of 2-unsubstituted and 2-alkylated 1,2-dihydroindol-3-ones followed by a formal [1,3] hydrogen shift afforded 3-alkylindoles, the formation of such a product **5** due to hydrogen shift was not observed except for **1c**. Therefore, in the present reaction, [3,3]-sigmatropic rearrangement of the intermediate **3** was preferable to the [1,3]-sigmatropic shift.

Further applications and studies on the stereochemistries of these tandem reactions are in progress.

Table 1 Tandem Wittig reaction and Cope rearrangement of 2-allyl-1,2-dihydroindol-3-ones

Entry	Indol-3-one **1**	Ylide **2**	Reaction[a] time/h	Product **4**	[Yield (%)[b]]
1	 **1a**	**2a**	5		**4a** R^1 = CO_2Me, R^2 = H (87%)
2		**2b**	6		**4b** R^1 = CO_2Bu^t, R^2 = H (78%)
3		**2c**	10		**4c** R^1 = CO_2Me, R^2 = Me (81%)
4		**2d**	40		**4d** R^1 = CN, R^2 = H (61%)
5	 **1b**	**2a**	14		**4e** R^1 = CO_2Me (58%)
6		**2e**	62		**4f** R^1 = COMe (58%)[c]
7		**2f**	72		**4g** R^1 = COPh (32%)[c]
8	 **1c**	**2a**	20		**4h** (34%)[d]

[a] The reaction was run in refluxing toluene. [b] Isolated yield. [c] Recovered **1b** (21%, entry 6; 61%, entry 7). [d] The Wittig product **3h** (50%) and 2-(2,3-dimethylallyl)indole acetate **5h** (16%) were also obtained.

We are grateful to the Science and Technology Agency of the Japanese Government for Special Coordination Funds.

Received, 8th November 1994; Com. 4/06818A

Footnotes

† *Selected spectroscopic data* for **4a**: IR ($CHCl_3$) ν/cm^{-1} 1702, 1453, 1384, 1353, 1332. ^1H NMR (270 MHz, $CDCl_3$, *J*/Hz) δ 2.63 (s, 3H), 2.70 (dddd, *J* 1.3, 6.6, 8.3, 14.2, 1H), 2.87 (dddd, *J* 1.3, 6.6, 7.3, 14.2, 1H), 3.70 (s, 3H), 3.93 (dd, *J*, 7.3, 8.3, 1H), 5.06 (ddd, *J* 1.3, 1.7, 10.2, 1H), 5.12 (ddd, *J* 1.3, 1.7, 17.2, 1H), 5.80 (ddt, *J* 6.6, 10.2, 17.2, 1H), 7.30 (dt, *J* 1.0, 7.6, 1H), 7.36 (ddd, *J* 1.0, 7.6, 7.9, 1H), 7.40 (s, 1H), 7.38 (dt, *J* 1.0, 7.6, 1H), 8.43 (br d, *J* 7.9 Hz, 1H). HRMS *m/z* 271.1200 (calc. $C_{16}H_{17}NO_3$ 271.1208).

‡ Satisfactory analytical and spectral data were obtained for all compounds.

References

1 S. J. Rhoads and N. R. Raulins, *Org. React.*, 1975, **22**, 1; R. P. Lutz, *Chem. Rev.*, 1984, **84**, 205; R. K. Hill, *Comprehensive Organic Synthesis*, ed. L. A. Paquette, Pergamon, Oxford, vol. 5, 1991, p. 785.

2 Y. Tamaru, T. Harada and Z. Yoshida, *J. Am. Chem. Soc.*, 1980, **102**, 2392; F. E. Ziegler and T.-F. Wang, *J. Am. Chem. Soc.*, 1984, **106**, 718.

3 F. E. Ziegler and J. J. Piwinski, *J. Am. Chem. Soc.*, 1982, **104**, 7181.

4 E. Piers, I. Nagakura and H. E. Morton, *J. Org. Chem.*, 1978, **43**, 3630; R. H. Bradburg, T. L. Gilchrist and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3225; L. Crombie and K. M. Mistry, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1981; E. J. Corey, A. Guzman-Perez and T.-P. Loh, *J. Am. Chem. Soc.*, 1994, **116**, 3611.

5 L. P. Paquette, *Synlett*, 1990, 67; *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 609; S. R. Wilson, *Org. React.*, 1993, **43**, 93; E. Lee, Y. R. Lee, B. Moon, O. Kwon, M. S. Shim and J. S. Yun, *J. Org. Chem.*, 1994, **59**, 1444.

6 R. K. Bramley and R. Grigg, *J. Chem. Soc., Chem. Commun.*, 1969, 99.

7 R. J. Sundberg, *The Chemistry of Indoles*, Academic, London, 1970; H. Ishibashi, N. Mita, N. Matsuba, T. Kubo, M. Nakanishi and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2821; K. Samizu and K. Ogasawara, *Synlett*, 1994, 499.

8 T. Kawasaki, Y. Nonaka, M. Kobayashi and M. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2445; T. Kawasaki, K. Masuda, Y. Baba, K. Takada and M. Sakamoto, *Chem. Pharm. Bull.*, 1994, **42**, 1974.

9 I. Gosney and A. G. Rowley, *Organophosphorous Reagents in Organic Synthesis*, ed. J. I. G. Cadogan, Academic, London, 1979, p. 17.

10 T. Kawasaki, Y. Nonaka, M. Uemura and M. Sakamoto, *Synthesis*, 1991, 701; T. Kawasaki, Y. Nonaka, H. Ohtsuka, H. Sato and M. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1101.