

On the Reaction of *N*-(3-Oxo-2-cyclohexenyl)imino]triphenylphosphorane with α -Bromo Ketones and α,β -Unsaturated Ketones¹⁾

Makoto NITTA,* Hironobu SOEDA, and Yukio IINO

Department of Chemistry, School of Science and Engineering, Waseda University, Shinjuku-ku, Tokyo 169
(Received July 12, 1989)

Synopsis. The thermal reaction of *N*-(3-oxo-2-cyclohexenyl)imino]triphenylphosphorane with α -bromo ketones and α,β -unsaturated ketones underwent an enamine-type alkylation and a subsequent aza-Wittig reaction to give substituted 1,5,6,7-tetrahydro-4*H*-indol-4-ones and 7,8-dihydro-5(6*H*)-quinolinones albeit in modest yields.

The reaction of tertiary phosphine with an organic azide to produce iminophosphorane is known as the Staudinger reaction.²⁾ However, the synthetic applications of the methodology for nitrogen heterocycles have attracted increasing attention only recently.³⁾ We have recently demonstrated a simple preparation of *N*-(vinylimino)phosphoranes,^{4–6)} which reacted with α -bromo ketones, α,β -unsaturated ketones, and tropone derivatives in an enamine alkylation process followed by an aza-Wittig reaction to provide novel routes to pyrroles,⁴⁾ pyridines,⁵⁾ and 1-azaazulene derivatives.⁶⁾ Although the *N*-(vinylimino)phosphorane is considered to be an equivalent for enamine, like enols, enamines are generally unstable and undergo a rapid conversion into the imine tautomer. Thus, simple enamines have no synthetic utility. However, β -amino enones are stable and easily isolated. A recent example, 3-amino-2-cyclohexen-1-one (**1**), has been widely used for the synthesis of 1,5,6,7-tetrahydro-4*H*-indol-4-ones and 7,8-dihydro-5(6*H*)-quinolinones.^{7a–e)}

In a search for more detailed behavior as well as synthetic utilities of *N*-(vinylimino)phosphoranes, and in comparison with the enamine **1**, we report here on the first example of a reaction of *N*-(3-oxo-2-cyclohexenyl)imino]triphenylphosphorane (**2**) with α -bromo ketones and α,β -unsaturated ketones to give 1,5,6,7-tetrahydro-4*H*-indol-4-ones and 7,8-dihydro-5(6*H*)-quinolinones.

Compound **2** was prepared by the established method (see Experimental). Although the *N*-(vinylimino)phosphorane derivatives are generally hydrolyzed easily to give the corresponding carbonyl compounds,⁶⁾ compound **2** is stabilized⁸⁾ and it is not hydrolyzed on a TLC plate. The ¹³C NMR signals due to β -carbon atoms of the enone moieties of **2** and **3** appear at higher fields, compared with that of the corresponding carbon atom of cyclohexenone (**4**)⁹⁾ (Fig. 1). Thus, a high electron density of the β -carbon atom as well as the possibility for an enamine-type alkylation of **2** were suggested.

The reaction of **2** with α -bromo ketones **5a–f** in the

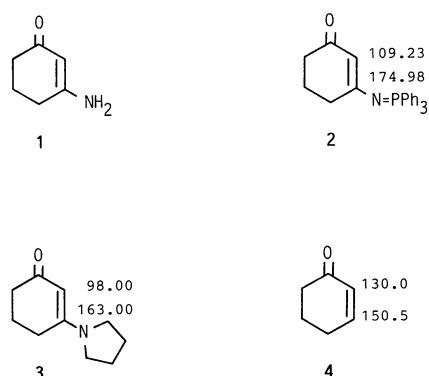
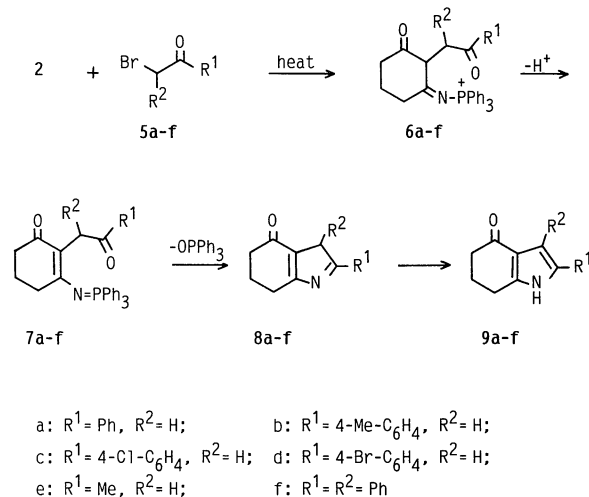


Fig. 1.



Scheme 1.

Table 1. Results for the Reaction of **2** with α -Bromo Ketones **5a–f** to give **9a–f**

Entry	5	Molar ratio of 5/2	Solvent	Reaction time/h	Product yield/%	Recovery of 5
1	5a	2.0	Dioxane	20	56	45
2	5b	1.2	Dioxane	27	28	63
3	5c	1.0	Dioxane	24	42	47
4	5d	1.0	Dioxane	23	38	—
5	5e	3.0	Dioxane	6	39	—
6	5f	1.2	Dioxane	60	6	—

Table 2. Results for the Reaction of **2** with α,β -Unsaturated Ketones **10a–f** to give **14a–d**

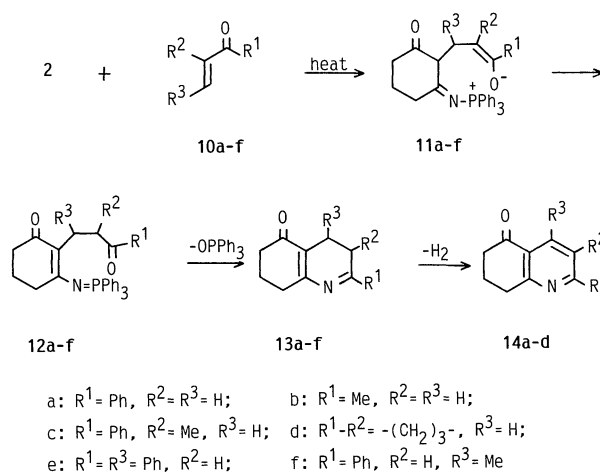
Entry	10	Molar ratio of 10/2	Solvent	Reaction time/h	Product yield/%	Recovery of 10
1	10a	1.0	Dioxane	27	52	—
2	10a	1.1	PhMe	24	52	—
3	10b	9.0	PhMe	96	60	—
4	10c	3.0	PhMe	150	18	84 ^{a)}
5	10d	2.0	PhMe	48	20	—
6	10e	1.0	Dioxane	168	0	100
7	10f	1.1	PhMe	168	0	100

a) A mixture of **10c** and its dimer (Ref. 10) in a ratio of 7/3.

presence of potassium carbonate gave 1,5,6,7-tetrahydro-4*H*-indol-4-ones **9a–f** (Scheme 1). The results are summarized in Table 1. In the reaction of **5f**, which has an additional substituent on the α -carbon atom, **9f** was produced in low yield (Entry 6). Although the results are very similar to those of *N*-(1-phenylvinylimino)phosphoranes with α -bromo ketones,⁴⁾ higher temperatures and prolonged heating were required for the reaction of **2**. Although no reaction of 3-amino-2-cyclohexen-1-one **1** with α -bromo ketones appeared, the reaction of **1** with **5a** in dioxane under refluxing gave **9a** in an 18% yield, which is even worse than those of Entry 1 (see Experimental). The structures of known compounds **9a,b** and **9e,f** were identified by comparisons of the physical data with those reported in the literature (see Experimental). Compounds **9c,d** were new and comparisons of physical data with those of **9a,b** and **9e,f** clearly supported the given structures.

Possible reaction sequences are also shown in Scheme 1. The initial step in an enamine-type alkylation of **2** onto **5a–f** to give **6a–f**, and subsequent deprotonation regenerate iminophosphoranes **7a–f**. Intermediates **7a–f** then undergo an intramolecular aza-Wittig reaction to give **8a–f**, of which aromatization gives **9a–f**. The low yield of **9f** may be ascribed to a steric hindrance of the phenyl group at the α -position in the enamine alkylation process.

On the other hand, the reaction of **2** with α,β -unsaturated ketones **10a–d** in toluene or in dioxane under refluxing with a complete consumption of **2** gave 7,8-dihydro-5(6*H*)-quinolinones **14a–d** (Scheme 2). The results are summarized in Table 2. The reaction of **2** with **10a,b**, both of which have no substituent at both the α - and β -positions, gave **14a,b** in moderate yields (Table 2, Entries 1–3). However, the reaction of **2** with **10c,d**, both of which are substituted at the α -carbon atom, gave **14c,d** in low yields; in the former case a dimerization¹⁰⁾ (Diels–Alder reaction) of **10c** occurred (Entry 4). Moreover, the attempted reaction of **2** with **10e,f**, both of which have a substituent at the β -carbon atom, gave no product, and enones **10e,f** were recovered quantitatively. This fact may be ascribed to a steric hindrance of the substituent at the β -position of **10e,f**. Thus, the reaction of **2** seems to be sensitive to a steric hindrance, as compared to those of *N*-(vinylimino)phosphoranes.^{4,5)} Compounds **14a–d** were known and their



Scheme 2.

structures identified by comparisons of the physical data with those reported in the literature (see Experimental).

The reaction sequences are also shown in Scheme 2.⁵⁾ The enamine alkylation of **2** to the β -carbon atom of **10a–d** initially occurs to give **11a–d**, and subsequent hydrogen migration regenerate iminophosphoranes **12a–d**. Intermediates **12a–d** then undergo an intramolecular aza-Wittig reaction to give dihydropyridines **13a–d**, which are dehydrogenated to give **14a–d** under the reaction conditions in the presence of Pd–C.

Although the reaction of *N*-vinyliminophosphorane **2** with α -bromo ketones and α,β -unsaturated ketones were clarified, no synthetic priority of **2** to **1** could be observed. Strong reaction conditions were required for **2**, as compared with the related reactions of *N*-(1-phenylvinylimino)phosphorane, probably because of the presence of an electron-withdrawing carbonyl group.

Experimental

The ¹H NMR spectra were recorded on a R-90H spectrometer. High-resolution mass spectral studies were conducted using a JEOL DX-300 spectrometer. All melting points are uncorrected.

Preparation of *N*-(3-Oxo-2-cyclohexenyl)imino]triphenylphosphorane (2**).** A solution of triphenylphosphine (8.38

g, 32 mmol) and 3-azido-2-cyclohexen-1-one (4.16 g, 32 mmol) in dry benzene (80 cm³) was stirred for 4 h under a nitrogen atmosphere. After the benzene was removed in vacuo, the residue was crystallized from benzene-hexane to give **2** (11.7 g, 95%): mp 150–152.5 °C (lit.⁸ 163–163.5 °C); ¹³C NMR (CDCl₃) δ=197.76, 174.98, 132.45, 132.17, 128.90, 128.12, 109.23, 36.37, 35.87, 22.65.

Preparation of 3-(1-Pyrrolidinyl)-2-cyclohexen-1-one (**3**).

A solution of 1,3-cyclohexandione (1.12 g, 10 mmol) and pyrrolidine (1.24 g, 17.5 mmol) in dry benzene (10 cm³) was refluxed by using a Dean-Stark apparatus for 5 h. After the usual workup, the enamine **3** was obtained: mp 83–85 °C (lit.¹¹ mp 86–88 °C); ¹³C NMR (CDCl₃) δ=195.44, 163.00, 98.00, 45.57, 35.56, 27.63, 24.72, 21.84.

General Procedure for the Reaction of 2 with α-Bromo Ketones 5a–f. A mixture of **2** (186 mg, 0.5 mmol), α-bromo ketones **5a–f**, and potassium carbonate (138 mg, 1 mmol) in dry dioxane was refluxed for a period with a complete consumption of **2** under nitrogen atmosphere. After the reaction mixture was filtered through Celite and concentrated, the residue was separated by TLC on silica gel to give pure samples of **9a–f**. In the isolation of **9a–c**, AcOEt-hexane (6/1) was used as a developer. In the isolation of **9d**, the TLC plates were developed five times by using AcOEt-hexane (1/1). In the case of **9e**, ethanol-hexane (1/6) was used as the developer. In the isolation of **9f**, AcOEt was used as the developer. Both the reaction conditions and the yields of the products are summarized in Table 1. For 2-phenyl-1,5,6,7-tetrahydro-4H-indol-4-one (**9a**): mp 227–228 °C (from ethanol) (lit.¹² 232 °C). For 2-(4-methylphenyl)-1,5,6,7-tetrahydro-4H-indol-4-one (**9b**): mp 275–277 °C (from methanol) (lit.¹³ 270 °C). For 2-(4-chlorophenyl)-1,5,6,7-tetrahydro-4H-indol-4-one (**9c**): mp 264–266 °C (from methanol); ¹H NMR (CDCl₃) δ=2.22 (2H, q, J=6.6 Hz), 2.52 (2H, t, J=5.9 Hz), 2.88 (2H, t, J=6.2 Hz), 6.80 (1H, d, J=2.9 Hz), 7.37 (4H, s), 8.45–8.65 (1H, broad s). Found: m/z 245.0628 and 247.0569. Calcd for C₁₄H₁₂ClNO: M, 245.0608 and 247.0578. For 2-(4-bromophenyl)-1,5,6,7-tetrahydro-4H-indol-4-one (**9d**): mp 277–279 °C (from methanol); ¹H NMR (CDCl₃) δ=2.23 (2H, q, J=5.6 Hz), 2.52 (2H, t, J=5.7 Hz), 2.88 (2H, t, J=5.8 Hz), 6.81 (1H, d, J=2.0 Hz), 7.32 (2H, d, J=9.0 Hz), 7.52 (2H, d, J=9.0 Hz), 8.40–8.65 (1H, broad s). Found: m/z 289.0081 and 291.0067. Calcd for C₁₄H₁₂BrNO: M, 289.0102 and 291.0082. For 2-methyl-1,5,6,7-tetrahydro-4H-indol-4-one (**9e**): mp 199–200 °C (from benzene) (lit.¹⁴ 210–211 °C). For 2,3-diphenyl-1,5,6,7-tetrahydro-4H-indol-4-one (**9f**): mp >300 °C (from methanol) (lit.¹⁵ 314–316 °C).

Reaction of 3-Amino-2-cyclohexen-1-one (1**) with 5a.** A mixture of **1** (33 mg, 0.3 mmol), **5a** (120 mg, 0.6 mmol), and potassium carbonate (83 mg, 0.6 mmol) in dry dioxane (2 cm³) was heated under reflux for 7 h with complete consumption of **1**. After the reaction mixture was filtered through Celite and concentrated, the residue was separated by TLC on silica gel using AcOEt as the developer to give **5a** (76 mg, 64%) and **9a** (11.3 mg, 18%), which was identical with the authentic specimen.

General Procedure for the Reaction of 2 with α,β-Unsaturated Ketones 10a–f. A mixture of **1** (186 mg, 0.5 mmol), **10a–f** and 5% Pd-C (0.025 g atom) in dry toluene or dioxane was refluxed under nitrogen atmosphere. After

the reaction mixture was concentrated, the residue was separated by TLC on silica gel. In the isolation of **14a,c**, AcOEt-hexane (3/1) was used as the developer. In the reactions of **10b** and **10d–f**, AcOEt-hexane (1/1) was used as the developer to give **14b**, **14d** or the starting materials, **10e–f**. The reaction conditions and the yields are summarized in Table 2.

For 2-phenyl-7,8-dihydro-5(6H)-quinolinone (**14a**): mp 126.5–127.5 °C (from ethanol) (lit.¹⁶ 121–122 °C). For 2-methyl-7,8-dihydro-5(6H)-quinolinone (**14b**):¹⁷ oil. For 3-methyl-2-phenyl-7,8-dihydro-5(6H)-quinolinone (**14c**): mp 69.5–70.5 °C (from ethanol) (lit.¹⁶ 70–71 °C). For 1,2,3,5,6,7,8-hexahydro-8H-cyclopenta[b]quinolin-8-one (**14d**): mp 58–59 °C (from cyclohexane) (lit.¹⁵ 60–61 °C).

References

- 1) Part 13 of the reaction of N-(vinylimino)phosphoranes. Part 12: M. Nitta, Y. Iino, and K. Kamata, *Heterocycles*, **29**, 1655 (1989).
- 2) Yu. G. Gololobov, I. N. Zhmurova, and L. F. Kasukhin, *Tetrahedron*, **37**, 437 (1981).
- 3) S. Eguchi, T. Okano, and H. Takeuchi, *Heterocycles*, **26**, 3265 (1987); H. Takeuchi, S. Yanagida, T. Ozaki, S. Hagiwara, and S. Eguchi, *J. Org. Chem.*, **54**, 431 (1989); M. Nitta and Y. Iino, *J. Chem. Soc., Perkin Trans. 1*, in press; and references cited therein.
- 4) Y. Iino, T. Kobayashi, and M. Nitta, *Heterocycles*, **24**, 2437 (1986).
- 5) T. Kobayashi and M. Nitta, *Chem. Lett.*, **1986**, 1549; Y. Iino and M. Nitta, *Bull. Chem. Soc. Jpn.*, **61**, 2235 (1988); N. Kanomata and M. Nitta, *Tetrahedron Lett.*, **29**, 5957 (1988).
- 6) M. Nitta, Y. Iino, E. Hara, and T. Kobayashi, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 51.
- 7) a) P. G. Baraldi, D. Simoni, and S. Manfredini, *Synthesis*, **1983**, 902; b) F. Yuste and R. S. Obregon, *J. Org. Chem.*, **47**, 3665 (1982); c) E. Reimann and J. M. Friesinger, *Arch. Pharm. (Weinheim, Ger.)*, **318**, 871 (1985); d) L. Rondahl, *Acta Pharm. Suec.*, **17**, 288 (1980); e) S. Torii, T. Inokuchi, and M. Kubota, *Synthesis*, **1986**, 400.
- 8) Y. Tamura, T. Miyamoto, J. Eiho, H. Taniguchi, T. Nishimura, and Y. Kita, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 105.
- 9) M. J. Loots, L. R. Weingarten, and R. H. Levin, *J. Am. Chem. Soc.*, **98**, 4571 (1976).
- 10) J. E. Mulvaney, J. G. Dillon, and J. L. Laverty, *J. Polym. Sci., Part A-1*, **6**, 1841 (1968).
- 11) E. J. Cone, R. H. Garner, and A. W. Hayes, *J. Org. Chem.*, **37**, 4436 (1972).
- 12) H. Stetter and E. Siehnhold, *Chem. Ber.*, **88**, 271 (1955).
- 13) A. N. Kost, L. G. Ovseneva, and T. G. Shuvaeva, *Khim. Geterotsikl. Soedin.*, **1966**, 717; *Chem. Abstr.*, **66**, 115537k (1967).
- 14) K. E. Schulte, J. Reisch, and H. Lang, *Chem. Ber.*, **96**, 1470 (1963).
- 15) C. Ruangsriyanand, H.-J. Rimek, and F. Zymalkowski, *Chem. Ber.*, **103**, 2403 (1970).
- 16) H. J. Roth and R. Troscheutz, *Arch. Pharm. (Weinheim, Ger.)*, **310**, 48 (1977).
- 17) A. C. W. Curran, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 975.