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Reaction of 2-Aroylcyclohex-2-enones with Hydroxylamine. Isoxazole Ring Formation

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A novel one-step and high-yield isoxazole formation of 2-aroylcyclohex-2-enones is described. Treatment of such an enone with hydroxylamine under acidic conditions ($NH_2OH \cdot HCl$ in EtOH) gave the corresponding 3-aryl-6,7-dihydro[2,1]benzisoxazole. Changes in the reaction conditions caused marked changes in the course of the reaction. A possible mechanism for these reactions is put forward.

Keywords——Isoxazole formation; 3-aryl-6,7-dihydro[2,1]benzisoxazole; masked β-dicarbonyl compounds; hydroxylamine; oximation under acidic conditions; Semmler-Wolff aromatization

Although the isoxazole ring (2) now has a major role as a masked β-dicarbonyl compound (1) or enaminoketone,[1] there have been quite few reports on the chemistry of isoxazoles (4) of β-dicarbonyl compounds (3) having a double bond between the carbonyl groups (Chart 1). Very recently, we reported[2] the preparation of the isoxazole of ethyl 1,4,5,6,7,8-hexahydro-4,5-dioxo-3-quinolinecarboxylate having such a β-dicarbonyl system by the standard method[3] using monooximation of the ketone followed by cyclization of the oxime, and successfully converted the isoxazole into the corresponding aromatized compound, 5-amino-1-ethyl-4-oxo-3-quinolinecarboxylic acid in several steps. We now have an interest in the preparation of isoxazole derivatives of 2-benzoyl-3-substituted cyclohex-2-enones as masked enones in the course of a study on the photocyclization of 2-aroyl-3-substituted cyclohex-2-enones[4] and examined various procedures, including the standard method described in the case of ethyl 1,4,5,6,7,8-hexahydro-4,5-dioxo-3-quinolinecarboxylate. In the present paper, we describe a novel one-step and high-yield isoxazole formation of 2-aroylcyclohex-2-enones (**5a**—**g**).

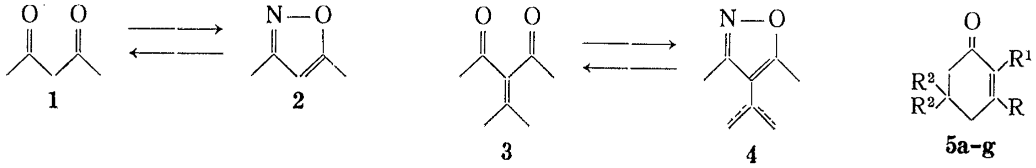


Chart 1

Initially, we examined the isoxazole formation of 2-benzoyl-3-methylcyclohex-2-enone (**5a**)[4] by the standard method: when the enone (**5a**) was treated with hydroxylamine hydrochloride–sodium acetate in aqueous ethanol, the monooxime (**6a**) and dioxime were obtained in 32% and 30% yields, respectively. Reaction of **6a** with ethyl chloroformate in the presence of pyridine followed by treatment with silica gel in benzene or heating of **6a** in ethanolic hydrogen chloride gave 4-methyl-3-phenyl-6,7-dihydro[2,1]benzisoxazole (**7a**), but the overall yield of **7a** from **5a** never exceeded 28%. Some changes in the reaction of conditions caused marked changes in the course of reaction of **5a** with hydroxylamine. Thus, treatment of **5a** with hydroxylamine under acidic conditions ($NH_2OH \cdot HCl$ in EtOH) gave a 72% yield of

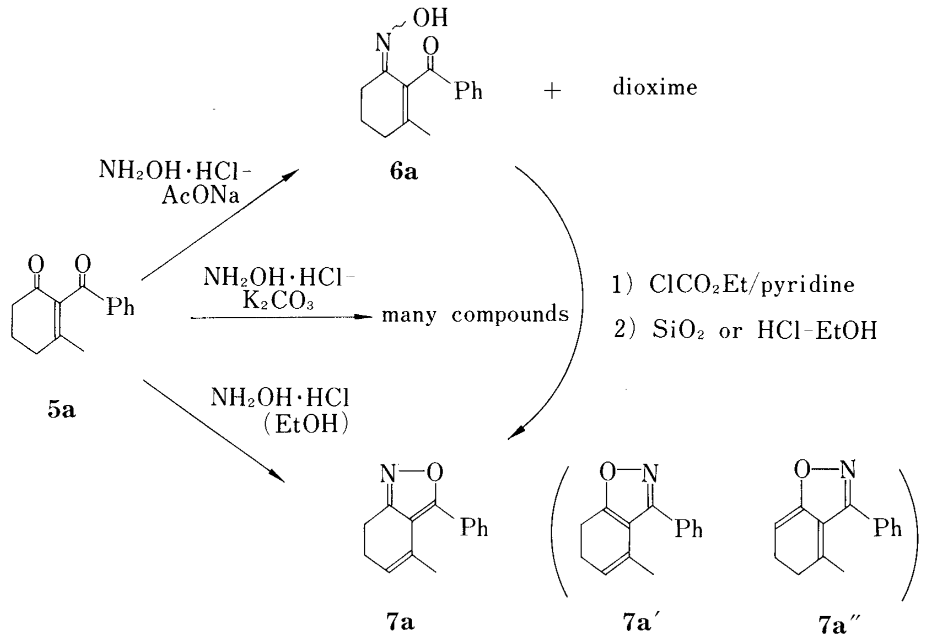


Chart 2

the isoxazole (**7a**) directly, although treatment under basic conditions ($NH_2OH \cdot HCl$–K_2CO_3 in aqueous EtOH) gave many compounds besides **6a** and the dioxime (Chart 2). The structure of **7a** was tentatively assigned from a consideration of the reactivity of both carbonyl groups in **5a** and the spectral data of **7a**. For instance, i) the carbonyl group of the cyclohexenone ring is much more active than that of the benzoyl group toward nucleophile and was selectively attacked by hydroxylamine and ii) in the spectra of **7a**, the disappearance of carbonyl absorptions in the infrared (IR) spectrum and the appearance of typical vinyl proton in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum were observed. Finally, the following chemical evidence excluded the other possible structures, **7a′** and **7a″** completely: treatment of **7a** with 1-ethoxyvinyl acetate in the presence of *p*-toluenesulfonic acid (*p*-TsOH) gave rise to the Semmler–Wolff aromatization[5] to give the corresponding N,N-diacetylaminobenzophenone (**8**).[6] A plausible mechanism for the formation of **8** is shown in Chart 3.

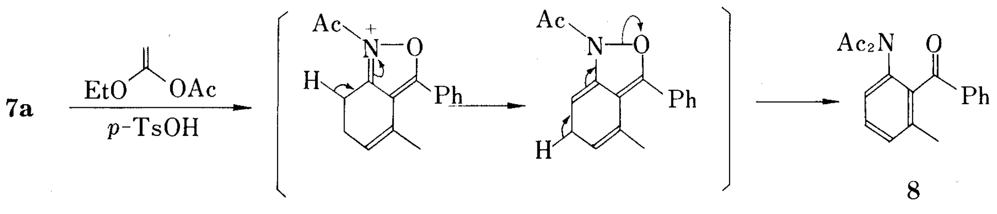
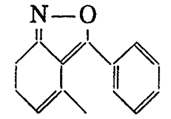
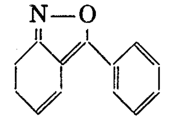
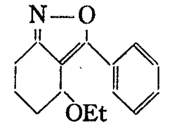
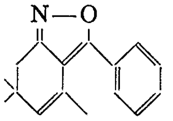
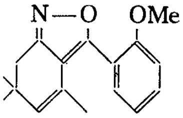
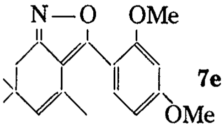
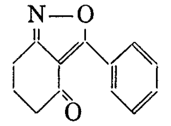
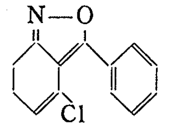
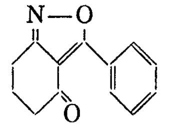
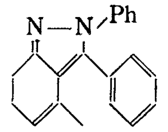


Chart 3

Similarly, we have undertaken an investigation on the direct isoxazole formation of other 2-aroylcyclohex-2-enones and have found that this method is remarkably effective for the conversion of **5b**—**g** to the desired isoxazoles (**7b**—**g**). Phenylhydrazine also reacted with **5a** in a similar fashion to give the corresponding pyrazole derivative (**7h**). The yields and spectral data are summarized in Tables I and II.

By analogy with the mechanism proposed for the reaction of cyclohexane-1,3-dione with hydroxylamine under acidic conditions in alcohol ($NH_2OH \cdot HCl$–ROH) leading to the corresponding 3-alkoxycyclohex-2-enone oxime (**10**),[7] it is likely that conversion of **5a**—**g** into **7a**—**g** proceeds *via* the initial formation of the monooxime (i), its isomerization to the intermediate, (ii) or (iii), and subsequent cyclization as indicated in Chart 4.

Table I. Isoxazole and Pyrazole Formation of 2-Aroylcyclohex-2-enones (**5a**—**g**)

Entry	Substrate				Reaction time (h)	Product **7**	Yield (%) of **4**
	5	R	R^1	R^2			
1	**5a**	CH_3	C_6H_5CO	H	2	 **7a**	72
2	**5b**	H	C_6H_5CO	H	2	 **7b**	28
						 **7b′**	22
3	**5c**	CH_3	C_6H_5CO	CH_3	7	 **7c**	94
4	**5d**	CH_3	$2\text{-}CH_3OC_6H_4CO$	CH_3	8	 **7d**	92
5	**5e**	CH_3	$2,4\text{-}(CH_3O)_2C_6H_3CO$	CH_3	7	 **7e**	87
6	**5f**	OH	C_6H_5CO	H	6	 **7f**	32
7	**5g**	Cl	C_6H_5CO	H	5	 **7g**	42
8	**5g**	Cl	C_6H_5CO	H	1.5	 **7f**[a]	95
9	**5a**	CH_3	C_6H_5CO	H	5	 **7h**	81

a) The reaction was performed in the presence of K_2CO_3.

Table II. Spectral Data for Isoxazoles and Related Compounds (**7a**—**h**)

Compounds **7**	IR ν_{max} (cm^{-1})	^1H-NMR δ ($CDCl_3$)	UV λ_{max}^{EtOH} (nm)
7a	1605, 1455, 1430	1.84 (3H, d, $J=1.5$ Hz, CH_3), 2.1—3.05 (4H, m, $CH_2\times2$), 5.45—5.80 (1H, m, CH), 7.20—7.75 (5H, m, ArH)	222, 276
7b	1640, 1590, 1570, 1440	2.40—3.10 (4H, m, $CH_2\times2$), 5.85—6.20 (1H, m, CH), 6.55—6.85 (1H, m, CH), 7.35—8.00 (5H, m, ArH)	215, 290

Compounds 7	IR ν_{max} (cm^{-1})	^{1}H-NMR δ (CDCl$_3$)	UV λ_{max}^{EtOH} (nm)
7b′	1640, 1625, 1460, 1450	1.25 (3H, t, J=7 Hz, CH$_3$), 1.55—3.00 (6H, m, CH$_2\times$3), 3.68 (2H, q, J=7 Hz, CH$_2$), 4.62 (1H, t, J=3Hz, CH), 7.30—7.60 (3H, m, ArH), 7.70—8.00 (2H, m, ArH)	252
7c	1635, 1590, 1445, 1420	1.13 (6H, s, CH$_3\times$2), 1.84 (3H, s, CH$_3$), 2.68 (2H, s, CH$_2$), 5.50 (1H, s, CH), 6.90—7.55 (5H, m, ArH)	220, 273
7d	1640, 1590, 1485, 1460	1.13 (6H, s, CH$_3\times$2), 1.65 (3H, s, CH$_3$), 2.69 (2H, s, CH$_2$), 3.80 (3H, s, OCH$_3$), 5.37 (1H, s, CH), 6.90—7.30 (4H, m, ArH)	212, 220sh
7e	1615, 1600, 1580, 1520	1.12 (6H, s, CH$_3\times$2), 1.67 (3H, s, CH$_3$), 2.68 (2H, s, CH$_2$), 3.78 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 5.35 (1H, s, CH), 6.45—6.65 (2H, m, ArH), 7.15—7.40 (1H, m, ArH)	250, 275
7f	1665, 1580, 1550	2.15—3.15 (6H, m, CH$_2\times$3), 7.50—7.70 (2H, m, ArH), 8.40—8.53 (3H, m, ArH)	292
7g	1630, 1580, 1420	2.40—3.00 (4H, m, CH$_2\times$2), 6.01 (1H, t, J=5 Hz, CH), 7.35—7.65 (5H, m, ArH)	215, 265
7h	1600, 1560, 1510, 1460 1450	1.56 (3H, s, CH$_3$), 2.20—3.15 (4H, m, CH$_2\times$2), 5.50 (1H, brs, CH), 7.16 (5H, s, ArH), 7.29 (5H, s, ArH)	283

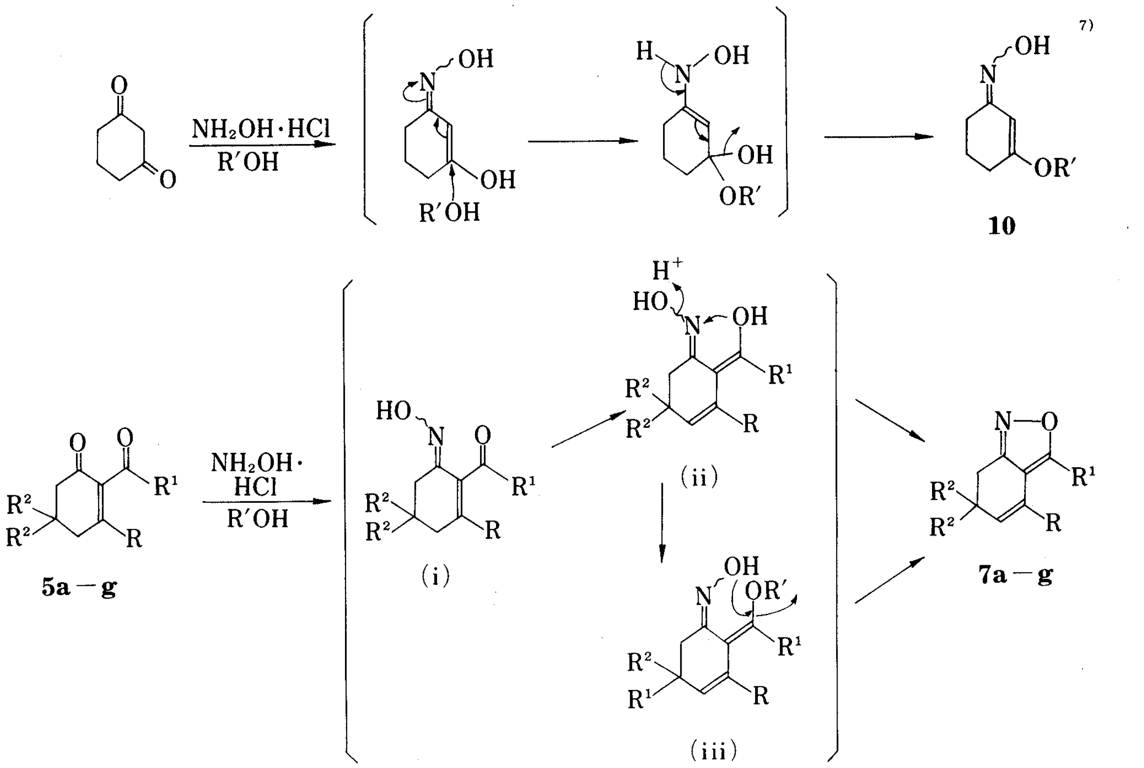


Chart 4

Experimental

All melting and boiling points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27G machine and NMR spectra on a Hitachi R-20A (60 MHz) or Hitachi R-22 (90 MHz) spectrometer (with tetramethylsilane as an internal standard). The ultraviolet (UV) absorption spectra were recorded on a Hitachi 124 instrument. Low and high resolution mass spectra (MS) were obtained with Hitachi RMU-6D and JEOL-JMS D-300 instruments, with a direct inlet system at 70 eV. Column chromatography was carried out on Merck Silica-gel 60.

Oximation of 2-Benzoyl-3-methylcyclohex-2-enone (5a) by the Standard Method——A solution of 2-benzoyl-3-methylcyclohex-2-enone (**5a**) (80 mg, 0.37 mmol), $NH_2OH \cdot HCl$ (40 mg, 0.54 mmol), and AcONa (46 mg, 0.58 mmol) in EtOH–H_2O (1: 1, 1 ml) was heated at 80°C for 8 h. After removal of the solvent *in vacuo*, the residue was partitioned between ether and water. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to preparative TLC on silica gel (benzene: ethyl acetate=5: 1 as the developing solvent) to give the monooxime (**6a**) and dioxime in 32 and 30% yields, respectively. **6a**: A pure sample was obtained by recrystallization from *n*-hexane, mp 127—130°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3310, 1660, and 1580; NMR (10% solution in $CDCl_3$) δ: 1.71 (3H, s, CH_3), 1.8—2.8 (6H, m, $CH_2 \times 3$), 7.3—7.6 (3H, m, ArH), and 7.8—8.1 (2H, m, ArH). Exact mass Calcd for $C_{14}H_{15}NO_2$: 229.1103. Found: 229.1105. Dioxime: Although this syrupy material shows one spot on TLC, the spectral data indicate the existence of tautomeric isomers. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1610, 1590, and 1470; NMR (10% solution in $CDCl_3$) δ: 1.90 (3H, s, CH_3), 2.00—2.95 (6H, m, $CH_2 \times 3$), 6.39 (1H, s, CH=), and 7.2—8.2 (5H, m, ArH). Exact mass Calcd for $C_{14}H_{16}N_2O_2$: 244.1212. Found: 244.1220.

Conversion of Monooxime (6a) into 4-Methyl-3-phenyl-6,7-dihydro[2,1]benzisoxazole (7a)——Ethyl chloroformate (6.5 mg, 0.06 mmol) was added dropwise to a solution of **6a** (10 mg, 0.04 mmol) and pyridine (5 mg, 0.06 mmol) in chloroform (1 ml). The reaction mixture was stirred at room temperature for 1 h and partitioned between water and chloroform. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was suspended in a mixture of SiO_2 (100 mg) and benzene (2 ml) and stirred at room temperature for 2 d. After removal of SiO_2 by filtration under reduced pressure, the filtrate was concentrated *in vacuo* to give 4-methyl-3-phenyl-6,7-dihydro[2,1]benzisoxazole (**7a**). An analytical sample was obtained by recrystallization from *n*-hexane, mp 62—65°C. *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.25; N, 6.63. Found: C, 79.48; H, 6.15; N, 6.62. MS *m/e*: 211 (M$^+$).

General Procedure for Conversion of 2-Aroylcyclohex-2-enones (5a—g) into 3-Aryl-6,7-dihydro[2,1]-benzisoxazoles (7a—g)——A solution of 2-aroylcyclohex-2-enone (5) and hydroxylamine hydrochloride in ethanol was heated under reflux for the period indicated in Table I. After removal of the solvent *in vacuo*, the residue was partitioned between water and chloroform. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. In many cases, the crude products obtained on removal of the solvent required purification by column chromatography or preparative TLC [*e.g.*, compounds **7a** and **7g**, silica gel (benzene); **7b** and **7b′**, silica gel (benzene: ethyl acetate=4: 1); **7c**, preparative TLC, silica gel (benzene: ethyl acetate=4: 1); **7d**, silica gel (benzene: ethyl acetate=4: 1); **7e** and **7f**, silica gel (chloroform)].

4-Methyl-3-phenyl-6,7-dihydro[2,1]benzisoxazole (7a)——This was prepared from **5a** (138 mg, 0.65 mmol) and $NH_2OH \cdot HCl$ (58 mg, 0.83 mmol) in EtOH (1 ml). This material was identical with an authentic specimen obtained from **6a**.

3-Phenyl-6,7-dihydro[2,1]benzisoxazole (7b) and 4-Ethoxy-3-phenyl-4,5,6,7-tetrahydro[2,1]benzisoxazole (7b′)——These compounds were prepared from **5b** (145 mg, 0.73 mmol) and $NH_2OH \cdot HCl$ (70 mg, 1.01 mmol) in EtOH (1 ml). **7b**: An analytical sample was obtained by recrystallization from *n*-hexane, mp 41—43°C. *Anal.* Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.06; H, 5.59; N, 7.11. MS *m/e*: 197 (M$^+$). **7b′**: A pure sample was obtained by distillation under reduced pressure, bp 135—150°C/2 mmHg (bath temperature). Exact mass Calcd for $C_{15}H_{17}NO_2$: 243.1283. Found: 243.1254.

3-Phenyl-4,6,6-trimethyl-6,7-dihydro[2,1]benzisoxazole (7c)——This was prepared from **5c** (22 mg, 0.09 mmol) and $NH_2OH \cdot HCl$ (7.4 mg, 0.11 mmol) in EtOH (1 ml). An analytical sample was obtained by recrystallization from *n*-hexane, mp 81—82.5°C. *Anal.* Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.46; H, 7.10; N, 5.91. MS *m/e*: 239 (M$^+$).

3-(2-Methoxy)phenyl-4,6,6-trimethyl-6,7-dihydro[2,1]benzisoxazole (7d)——This was prepared from **5d** (251 mg, 0.98 mmol) and $NH_2OH \cdot HCl$ (84 mg, 1.2 mmol) in EtOH (1.5 ml). An analytical sample was obtained by distillation under reduced pressure, bp 140—150°C/5 mmHg (bath temperature). *Anal.* Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.60; H, 7.05; N, 5.17. MS *m/e*: 269 (M$^+$).

3-(2,4-Dimethoxy)phenyl-4,6,6-trimethyl-6,7-dihydro[2,1]benzisoxazole (7e)——This was prepared from **5e** (270 mg, 0.89 mmol) and $NH_2OH \cdot HCl$ (80 mg, 1.15 mmol) in EtOH (1.5 ml). An analytical sample was obtained by recrystallization from *n*-hexane, mp 94—96°C. *Anal.* Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.16; H, 7.11; N, 4.75. MS *m/e* 299 (M$^+$).

4-Oxo-3-phenyl-4,5,6,7-tetrahydro[2,1]benzisoxazole (7f)——i) from **5f**: **7f** was prepared from **5f** (98 mg, 0.45 mmol) and $NH_2OH \cdot HCl$ (40 mg, 0.58 mmol) in EtOH (1 ml). An analytical sample was obtained by recrystallization from *n*-hexane, mp 65—67.5°C. *Anal.* Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.17; H, 5.11; N, 6.59. MS *m/e*: 284 (M$^+$).

ii) from **5g**: **7f** was prepared from **5g** (235 mg, 1 mmol), $NH_2OH \cdot HCl$ (83.4 mg, 1.2 mmol) and K_2CO_3 (280 mg, 2.0 mmol) in EtOH–H_2O (4: 1, 5 ml). The crude product was recrystallized from *n*-hexane to obtain a pure sample, which was identical with an authentic sample obtained above.

4-Chloro-3-phenyl-6,7-dihydro[2,1]benzisoxazole (7g)——This was prepared from **5g** (230 mg, 0.98 mmol) and $NH_2OH \cdot HCl$ (90 mg, 1.30 mmol) in EtOH (1 ml). An analytical sample was obtained by recrystallization from *n*-hexane, mp 72—73.5°C. *Anal.* Calcd for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05. Found: C, 67.15; H, 4.31; N, 6.02. MS *m/e*: 231, 233 (M^+).

6,7-Dihydro-2,3-diphenyl-4-methyl-2H-indazole (7h)——This was obtained from **5a** (121 mg, 0.5 mmol) and $C_6H_5NHNH_2 \cdot HCl$ (86.8 mg, 0.6 mmol) in EtOH (1.5 ml). An analytical sample was obtained by recrystallization from *n*-hexane, mp 114.5—116.5°C. *Anal.* Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.65; H, 6.32; N, 9.87. MS *m/e*: 286 (M^+).

Conversion of 7a into 2-Acetamido-6-methylbenzophenone (9)——A solution of **7a** (100 mg, 0.47 mmol) and *p*-TsOH (6 mg, 0.03 mmol) in 1-ethoxyvinyl acetate (0.4 ml) was heated at 80—90°C for 1 h under argon, concentrated *in vacuo*, and partitioned between water (10 ml) and chloroform (30 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to preparative TLC on silica gel (*n*-hexane: benzene: ethyl acetate= 1: 4: 4 as the developing solvent) to give a 51% yield (70 mg) of the N,N-diacetylamino compound (**8**). A pure sample was obtained by recrystallization from *n*-hexane, mp 85—88°C. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720 and 1680; NMR (10% solution in $CDCl_3$) δ: 2.13 (9H, s, CH_3 and $COCH_3 \times 2$), and 6.9—7.9 (8H, m, ArH). The compound (**8**) was used directly for deacetylation without recrystallization. Stirring of **8** with silica gel (300 mg) in warm methanol (0.5 ml) for a few days gave the crude acetanilide **9**. A pure sample was obtained by column chromatography on silica gel (benzene as the eluting solvent) followed by recrystallization from methanol, mp 143—144.5°C. *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.85; H, 5.85; N, 5.59. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}; 1680 and 1650; NMR (10% solution in $CDCl_3$) δ: 1.95 (3H, s, CH_3), 2.07 (3H, s, $COCH_3$), and 6.8—8.0 (9H, m, ArH and NH); MS *m/e*: 253 (M^+).

References and Notes

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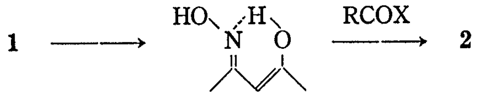
2) Y. Tamura, M. Fujita, L.C. Chen, K. Ueno, and Y. Kita, *J. Heterocyclic Chem.*, in press.

3) Generally, oximation of the β-dicarbonyl compound (**1**) gives the H-bonded enol form of the monooxime (**A**), which has the Z-configuration and is resistant to further attack by hydroxylamine. Cyclization of **A** by heating with acyl halide produces the isoxazole (**2**)



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