HETEROCYCLES, Vol. 23, No. 1, 1985

THE FACILE ONE POT SYNTHESIS OF 6-SUBSTITUTED 2(1H)-QUINOXALINONES

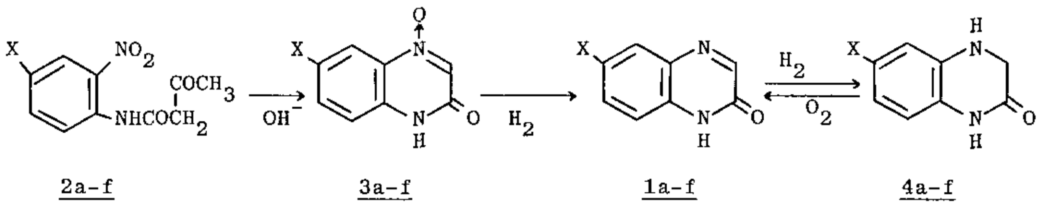
Gozyo Sakata,* Kenzi Makino, and Katsushi Morimoto
Central Research Institute, Nissan Chemical Ind., Ltd.
Tsuboi-cho, Funabashi, Chiba 274, Japan

Abstract - Facile one pot synthesis of 6-substituted 2(1H)-quinoxalinones and these reaction mechanisms are described. The intramolecular cyclization reaction of 4'-substituted 2'-nitroacetoacetanilides in aqueous basic medium and the reduction of 6-substituted 2(1H)-quinoxalinone-4-oxide with sodium borohydride or sodium hydrogensulfite were studied in detail.

6-Substituted derivatives of 2(1H)-quinoxalinones (1b-f) are known as intermediates for the synthesis of pharmaceutical and agricultural chemicals,[1-3] for instance, 1b-f can be used as intermediates for a new type of selective herbicides.[1,4] Several synthetic methods have been reported for the synthesis of unsubstituted 2(1H)-quinoxalinone (1a).[5-8] One of the facile and efficient methods is the intramolecular cyclization reaction of 2'-nitroacetoacetanilide (2a) followed by reduction of 2(1H)-quinoxalinone-4-oxide (3a) to 1a.[5,9] However, an extensive study for the syntheses of 1b-f from 2b-f, particularly in one pot reaction, has not been reported. Tennant[5] has reported that the cyclization reaction of 2a in aqueous potassium hydroxide affords 3a in low yield together with several by-products. Generally, the cyclization reaction of 2a to 3a is promoted in basic conditions[5] but the reaction conditions and the mechanism have not been studied in detail. Meanwhile, the reduction of 3a to 1a has reported by using of triphenylphosphine, sodium dithionite, hydrogenation in the presence of Pd catalyst or metal reduction with iron or tin in acidic medium.[5,9,10] However, the reduction of 3a by these reagents except triphenylphosphine gave a mixture of 1a and 3,4-dihydro-2(1H)-quinoxalinone (4a).

On the other hand, the reduction of 3c by triphenylphosphine gave 1c at reaction temperature more than 180 °C.[10] Now we studied the synthesis of 1b-f from 2b-f via 3b-f in detail and elaborated a facile method for the synthesis of 1b-f in one pot reaction.

In the first, cyclization reaction of 2b-f to 3b-f and the reduction of 3b-f to 1b-f were studied separately, and combined these reactions in one pot reaction. The reaction pathway is illustrated in Scheme 1.



X: a=H, b=F, c=Cl, d=Br, e=CF_3, f=OCH_3

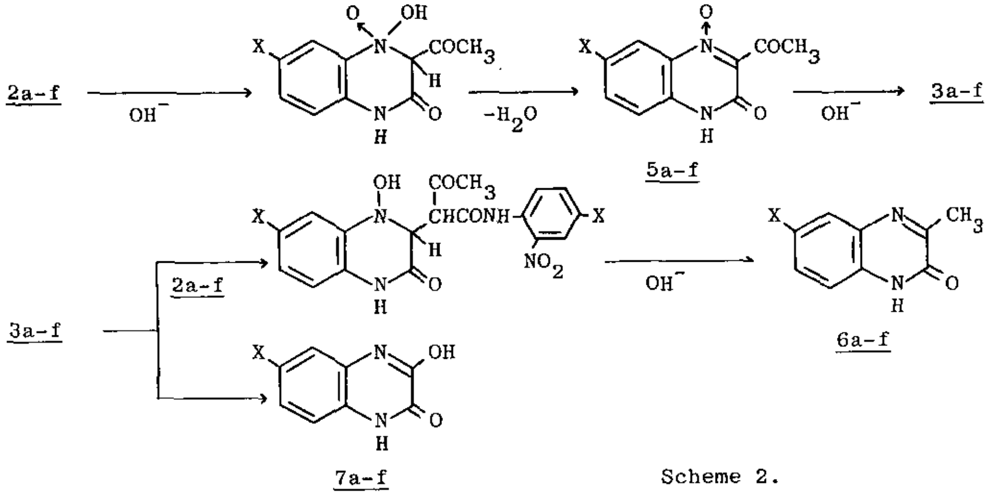
Scheme 1.

Compounds 2b-f were easily synthesized in good yields from 4-substituted 2-nitroanilines with diketene[11,12] in the presence of triethylamine or pyridine in an aromatic hydrocarbon as a solvent.

The intramolecular cyclization reaction of 2b-f was found to be influenced by several factors such as kinds of bases, molar ratio of bases, solvents, reaction temperatures and reaction times.

When sodium hydroxide or potassium hydroxide was used between three fold and seven fold equivalent to 2c in 5-20% aqueous solution, 2c was converted into 3c in the best yield shown in Table 1. But with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), 2c gave 3-acetyl-6-chloro-2(1H)-quinoxalinone-4-oxide (5c) in 52% yield. With calcium hydroxide or barium hydroxide, two unique by-products, 6-chloro-3-methyl-2(1H)-quinoxalinone (6c) and 6-chloro-3-hydroxy-2(1H)-quinoxalinone (7c) were formed in this reaction. It seemed that the former was derived from the intermolecular condensation of 3c with a carbanion of 2c and the latter from the intramolecular rearrangement of 3c.[13]

The reaction mechanism is assumed as Scheme 2.



Scheme 2.

The cyclization reaction was generally exothermic. The reaction temperature was maintained between 60-70 °C. At higher temperature (>80 °C), the side reactions occurred and polymerized unidentified materials were obtained. In the case of lower temperature than 60 °C, the reaction was extremely slow. After the reaction was over, the crude reaction mixture was acidified with diluted hydrochloric acid to isolate 3c. In this procedure, the analytical value of 3c in isolated product with HPLC internal standard method was about 10-15% lower than that of 3c in the crude reaction mixture. It was confirmed that the N-oxide easily rearranged to 3-position of quinoxaline ring in acidic conditions and the content of 7c increased in the course of the isolating procedure. Furthermore, 3c was isolated accompanying with other unidentified acidic materials and inorganic salts, so purification by ordinary method was very difficult. The results of the cyclization reaction of 2c at 60 °C under various conditions are summarized in Table 1.

Most of the reduction of 3b-f was investigated under aqueous basic conditions. Conventional catalytic hydrogenation of 3b-f in the presence of Pd-C or Raney-Ni afforded 1b-f and 3,4-dihydro-2(1H)-quinoxalinone (4b-f). Although 4b-f could be smoothly converted into 1b-f by oxidation with hydrogen peroxide or air,[9,10,14,15] the total yields of 1b-f were low.

Next, we investigated the reduction of 3c with chemical reducing agents such as zinc, iron, sodium dithionite, sodium hydrogensulfite or sodium borohydride under aqueous basic conditions. When metal reduction of 3c employing zinc or iron was

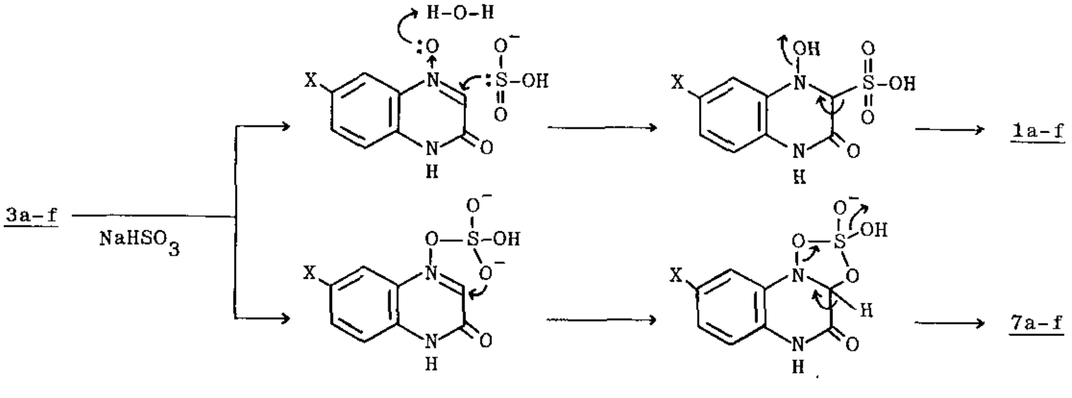
Table 1. The Cyclization Reaction of 2c to 3c[a)]

Base	Molar ratio base/2c	Reaction time(h)	Yield(%)[b)]			
			3c	7c	6c	5c
LiOH	6	0.5	77(65)[c)]	3	4	0
KOH	3	1.0	89(72)	0	0	0
KOH	7	0.5	95(86)	0	0	0
NaOH	3	1.5	90(81)	0	0	0
NaOH	7	1.0	94(84)	0	0	0
$Ca(OH)_2$	3	10.0	16	1	2	0
$Ba(OH)_2$	3	9.0	68	7	3	0
D.B.U.	3	5.0	5	3	4	52
Pyridine	3	5.0	trace	0	0	0

a) Water was used seven folds weight of 2c. b) Yields were determined with HPLC internal standard method using the crude reaction mixture.
c) ( ): Analytical value of isolated crude product with HPLC i. s. method.

carried out, 1c was obtained together with 4c. Compound 4c was converted into 1c but the total yield was not satisfactory.

Compound 1c was afforded in a low yield with sodium dithionite. Other types of reducing agents for the reduction of 3c were examined and it was found that sodium hydrogensulfite and sodium borohydride were satisfactory reducing agents. When sodium hydrogensulfite was used between two fold and three fold equivalent to 3c, compound 1c was obtained in 80-90% yield and a small amount of 7c was also obtained as by-product. It is shown in Scheme 3. In this reducing procedure, the analytical value of 1c in the crude reaction mixture was identical with that of isolated products. The results are summarized in Table 2.



Scheme 3.

Table 2. The Reduction Products of 3c to 1c

Reducing agent[a]	Yield(%)[b]			
	1c	4c	7c	1a
H_2/Pd-C	72.5(71.8)[c]	9.6	0	4.8
Zn	77.8(77.0)	1.2	0	0.6
$Na_2S_2O_4$	57.8(56.0)	0	3.8	0
$NaHSO_3$	86.2(85.8)	0	4.4	0
Na_2SO_3	85.7(85.0)	0	4.1	0
$NaBH_4$	94.2(93.8)	1.2	0	0

a) All reactions were carried out in aqueous sodium hydroxide. b) Yields were determined with HPLC internal standard method using crude reaction mixture. c) ( ): Analytical value of isolated product.

As mentioned in cyclization reaction of 2c, compound 3c was easily converted to 7c and unidentified materials in the isolating procedure. One pot synthesis of 1b-f were studied using best reagent of each reaction without isolating and purification of the intermediates 3b-f and satisfactory yields of 1b-f from 2b-f were obtained. Conditions and results are summarized in Table 3.

Table 3. One Pot Synthesis of 1b-f from 2b-f

Starting material	Product	Reaction conditions		Total yield(%)[c]
		Base for cyclization[a]	Reduction reagent[b]	
2b	1b	NaOH	$NaBH_4$	81
		KOH	$NaHSO_3$	72
2c	1c	NaOH	$NaBH_4$	84
		KOH	$NaHSO_3$	75
2d	1d	NaOH	$NaBH_4$	83
		NaOH	$NaHSO_3$	76
2e	1e	KOH	$NaBH_4$	79
		KOH	$NaHSO_3$	71
2f	1f	NaOH	$NaBH_4$	84
		NaOH	$NaHSO_3$	71

a) Base were used six molar equivalent to the starting materials.
b) $NaBH_4$ and $NaHSO_3$ were used 0.6 and three molar equivalent of the starting material, respectively. c) Yields were determined with HPLC internal standard method using isolated products.

EXPERIMENTAL SECTION

Ir spectra were measured on a JASCO A-3 Infrared Spectrophotometer. Mass spectra were measured on a JEOL D-300, JMA 3500 and DX-300, JMA 3100. Elemental analyses were measured on an Elemental Analyzer model 1106 (Carlo Erba Strumentazione). Chemical purities were determined on a Shimazu Liquid Chromatograph LC-3A. All melting points are uncorrected.

General procedure of one pot synthesis of 1b-f from 2b-f.

Sodium borohydride method: 2b-f (100 mmol) was added to 20% KOH (143 ml) or 16% NaOH (128 ml) and stirred at 60-65 °C for 1.5 h. The reaction mixture was cooled to 30 °C and diluted with water (150 ml). $NaBH_4$ (60 mmol) was added to a well-stirred solution at 25-30 °C and the stirring was continued for 1.5 h. Ice (300 g) was added to the reaction mixture, and acidified with 6N HCl at the temperature below 20 °C. The white solid was collected, washed with water, and dried.

It was analyzed by the measurement of HPLC using the standard sample. The results are shown in Table 3. Purification of 1b-f was carried out by the recrystallization of their sodium salts from water.

1b; mp >300 °C. ir(KBr): 2850, 1685, 1487, 1420, 1250, and 588 cm^{-1}. ms m/z 164 (M^+, base peak), 136, and 109. Found: C, 58.01; H, 2.96; N, 17.31%. Calcd for $C_8H_5N_2OF$: C, 58.84; H, 3.05; N, 17.07%.

1c; mp >300 °C. ir(KBr): 2825, 1680, 1472, 1408, and 887 cm^{-1}. ms m/z 180(M^+, base peak) and 152. Found: C, 52.95; H, 2.85; N, 15.39%. Calcd for $C_8H_5N_2OCl$: C, 53.18; H, 2.77; N, 15.15%.

1d; mp 298-300 °C. ms m/z 224(M^+, base peak), 196, and 117. Found: C, 42.75; H, 2.18; N, 12.29%. Calcd for $C_8H_5N_2OBr$: C, 42.67; H, 2.22; N, 12.44%.

1e; mp 256-258 °C. ir(KBr): 2860, 1695, 1640, 1319, 1182, and 1140 cm^{-1}. ms m/z 214(M^+, base peak), 195, 186, and 167. Found: C, 50.38; H, 2.18; N, 13.14%. Calcd for $C_9H_5N_2OF_3$: C, 50.47; H, 2.34; N, 13.08%.

1f; mp 267-269 °C. ms m/z 176(M^+, base peak), 161, 148, and 133. Found: C, 61.18; H, 4.45; N, 15.85%. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.55; N, 15.91%.

Sodium hydrogensulfite method: 2b-f (100 ml) was added to 20% KOH (143 ml) or 16% NaOH (128 ml) and stirred at 60-65 °C for 1.5 h. The reaction mixture was cooled to room temperature and diluted with water (150 ml).

Next, saturated $NaHSO_3$ (300 ml) solution was added to this well-stirred solution at 10-15 °C and stirring was continued for 1.5 h. Insoluble substances were filtered off and the filtrate was acidified with 6N HCl. The acidic solution was partly evaporated under reduced pressure and the resulting white solid was collected. It was washed with water and dried in vacuo. The results are shown in Table 3.

Cyclization reaction of 2c to 3c.

Potassium hydroxide method: A suspension of 2c (25 g, 97.5 mmol) in 18% KOH (184 ml) was stirred at 60-65 °C for 20 min and the resulting homogenous solution was cooled to room temperature. A small amount of insoluble substances was filtered off and the filtrate was diluted with water (410 ml), and acidified with 6N HCl below 20 °C. The resulting reddish solid was collected, washed with water, and dried in vacuo. It was analyzed by the measurement of HPLC using standard sample (Table 1). 3c; yield 86%, mp >300 °C. ir(KBr): 3050, 1660(CO), 1252(N-O), and 836 cm^{-1}. ms m/z 196(M^+, base peak), 180, 166, 152, 125, and 105. Found: C, 48.71; H, 2.45; N, 14.21%. Calcd for $C_8H_5N_2O_2Cl$: C, 48.85; H, 2.54; N, 14.25%.

Sodium hydroxide method: A suspension of 2c (25 g, 97.5 mmol) in 13.5% NaOH (175 ml) was stirred at 60-65 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with water (400 ml), and acidified with 6N HCl. The resulting reddish solid was collected, washed with water, and dried in vacuo. 3c; yield 84% (Table 1).

Reduction of 3c to 1c.

Hydrogen/Pd-C reduction: A suspension of 3c (11.1 g, 56.6 mmol) in ethanol (650 ml) was hydrogenated catalytically with 10% Pd-C (560 mg) at room temperature until 91.5 mmol of hydrogen had been absorbed. 1N NaOH (300 ml) was added to the reaction mixture and catalyst was filtered off. The solvent was partly evaporated under reduced pressure and the resulting reddish solid was filtered off. 3.5% H_2O_2 (115 ml) was added to the filtrate and warmed at 70-80 °C for 2.5 h. After cooling, acetic acid was added and the resulting white solid was collected, washed with water, and dried in vacuo. It was analyzed by measurement of HPLC using the standard sample (Table 2). 1c; yield 71.8%.

Zinc reduction: Zinc powder (30.6 g, 468 mmol) was added to a well-stirred solution of 3c (74 g, 377 mmol) in 5% NaOH (1250 ml) at 30-40 °C. After stirring for 10 min, 18% NaOH (540 ml) was added dropwise and stirring continued at 40-45 °C for 2.5 h. Active carbon (20 g) was added to the reaction mixture and it was cooled to room temperature. After filtering off active carbon and insoluble substances, ice (400 g) was added to the filtrate and the basic solution was acidified with 6N HCl. The resulting white solid was collected, washed with water, and dried *in vacuo*. 1c; yield 77.0%.

Sodium dithionite reduction: $Na_2S_2O_4$ (6.0 g, 34.5 mmol) was added to a well-stirred solution of 3c (3.0 g, 15.3 mmol) in 2% NaOH (30 ml) at room temperature. After stirring for 4 h, 5% NaOH (100 ml) was added and insoluble substances were filtered off. The basic solution was acidified with 2N HCl and partly evaporated under reduced pressure. 2N HCl was added furthermore and the resulting white solid was collected. It was washed with water, and then with acetone and dried *in vacuo*. 1c; yield 56.0%.

Sodium hydrogensulfite reduction: 3c (3.93 g, 20 mmol) was dissolved in 3.2% NaOH (25 ml) and saturated $NaHSO_3$ (6.24 g, 60 mmol) solution was added dropwise at room temperature. After stirring for 1 h, insoluble substances were filtered off and the filtrate was acidified with 4N HCl. The acidic solution was partly evaporated under reduced pressure and cooled to 0-5 °C. The resulting solid was collected, washed with water, and dried *in vacuo*. 1c; yield 85.8%.

Sodium borohydride reduction: $NaBH_4$ (0.40 g, 10.5 mmol) was added to the solution of 3c (3.93 g, 20 mmol) in 5% NaOH (20 ml) at room temperature. After stirring for 1.5 h, the reaction mixture was diluted with water (20 ml) and acidified with 2N HCl. The resulting white solid was collected, washed with water, and dried *in vacuo*. 1c; yield 93.8%. (Table 2).

ACKNOWLEDGMENT

The authors wish to express their thanks to Dr. Yasukazu Ura, General Manager of Central Research Institute, Nissan Chemical Industries Ltd., for his continuing guidance and encouragement.

REFERENCES

1. Y. Ura, G. Sakata, K. Makino, Y. Kawamura, T. Ikai, and Y. Kawamura, Ger. Offen. 3004770 (1980); Chem. Abstr., 1981, **94**, 103421h.
2. W. C. Lumma, Jr., R. D. Hartman, W. S. Saari, E. L. Engelhardt, V. J. Lotti, and C. A. Stone, J. Med. Chem., 1981, **24**, 93.
3. G. A. Carter, T. Clark, C. S. James, and R. S. T. Loeffler, Pestic. Sci., 1983, **14**, 135.
4. G. Sakata, K. Makino, Y. Kawamura, Y. Ura, T. Ikai, and Y. Kawamura, 10th International Congress of Plant Protection of England, Brighton, November 1983, Abstr., No. 2C-S4.

5. G. Tennant, J. Chem. Soc., 1963, 2428.

6. F. J. Wolf, K. Pfister, R. H. Beulel, R. M. Wilson, Jr., C. A. Robinson, and J. R. Stevens, J. Am. Chem. Soc., 1949, **71**, 6.

7. O. Hinsberg, Ber., 1884, **18**, 1228.

8. J. K. Lanquist, J. Chem. Soc., 1953, 2816.

9. R. Fusco and S. Rossi, Chim. Ind. (Milan)., 1963, **45**, 834. Chem. Abstr., 1964, **60**, 10683e.

10. R. Fusco and S. Rossi, Gazz. Chim. Ital., 1964, **94**, 3. Chem. Abstr., 1964, **61**, 4352b.

11. B. Miller and J. B. English, U. S. Patent 3708508 (1973); Chem. Abstr., 1973, **78**, 84448y.

12. R. N. Lacey and E. E. Connolly, Brit. Patent 715896 (1954); Chem. Abstr., 1955, **49**, 13290d.

13. G. Tennant, J. Chem. Soc., 1964, 1986.

14. R. L. Wear and C. S. Hamilton, J. Am. Chem. Soc., 1950, **72**, 2893.

15. G. T. Newbold and F. S. Spring., J. Chem. Soc., 1948, 519.

Received, 21st September, 1984