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Facile Synthesis of 2,4-Dioxo-1,2,3,4-tetrahydroquinazolines by Sulfur-Assisted Carbonylation with Carbon Monoxide

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ABSTRACT

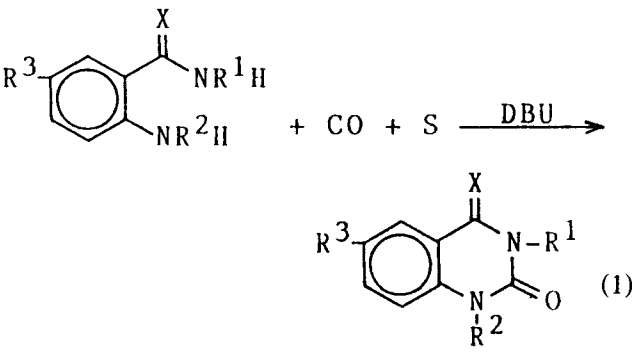
2,4-Dioxo-1,2,3,4-tetrahydroquinazolines were easily synthesized in excellent yields by sulfur-assisted carbonylation of 2'-aminobenzamides with carbon monoxide in the presence of a base, such as DBU or DBN.

INTRODUCTION

The carbonylation of amides with carbon monoxide has usually been performed in the presence of a transition metal catalyst. For example, the synthesis of imides from amides using a cobalt [1] and palladium catalyst [2] was reported. However, studies of this carbonylation of amides promoted by nontransition metal elements have been almost unexplored.

The sulfur-assisted carbonylation of amines with carbon monoxide to synthesize urea derivatives [3] and *S*-alkyl thiolcarbamates [4] was discovered about thirty years ago. Recently, our extensive studies of this carbonylation of other substrates having relatively weak nucleophilicities have led us to the successful development of a cyclic urea synthesis from aromatic amines [5], synthesis of thiolcarbonates [6] or carbonates [7] from alcohols, synthesis of dithiocarbonates from water [8], and carbonylation of active methylene compounds [9]. However, the carbonylation of amides using carbon monoxide could hardly be performed by hitherto known methods because of their low nucleophilicities.

We now wish to report a new and convenient synthesis of 2,4-dioxo-1,2,3,4-tetrahydroquinazolines (**1**) through the first example of carbonylation of aromatic amides with carbon monoxide promoted by elemental sulfur in the presence of an appropriate base (Equation 1).



(1)

1 X=O, S

RESULTS AND DISCUSSION

Examination of the reaction conditions for this carbonylation using 2-aminobenzamide as a starting substrate showed that the nature of the base and

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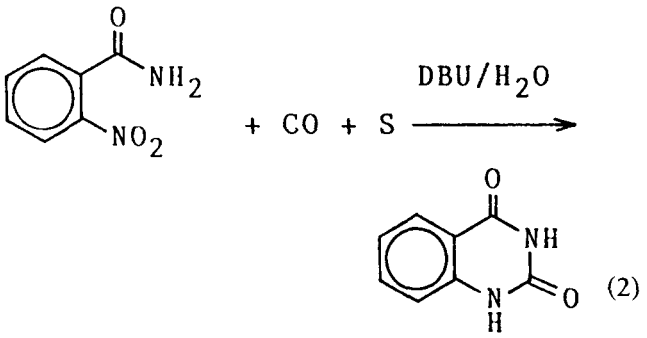
the reaction temperature produced remarkable effects (Table 1), and that the reaction took place smoothly at 80°C in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or DBN (1,5-diazabicyclo[4.3.0]non-5-ene) to give 2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**1a**) almost quantitatively. The COS–DBU complex, which proved to be a thermally unstable white solid that regenerated carbonyl sulfide on warming to 45°C, was formed from COS and DBU [10]. The excellent effect of DBU for carbonylation of 2-aminobenzamide can be understood on the basis that the COS–DBU complex might act as an active COS-transfer species.

Substituted 2,4-dioxo-1,2,3,4-tetrahydroquinazolines (**1a–g**) were synthesized by the carbonylation of the corresponding 2-aminobenzamides with carbon monoxide and sulfur in the presence of DBU under similar conditions (80°C, 30 kg/cm^2) (Table 2). Mostly, quinazolines (**1a–c, 1e–g**) were obtained in excellent yields. However, 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**1d**) was not obtained, presumably because of the steric hindrance of the two methyl groups.

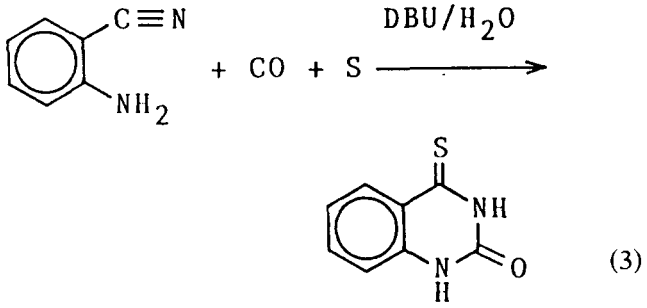
It was also found that both reduction of a nitro group and carbonylation of an amide group were accomplished in a one-pot operation by addition of water (10 mmol, 0.18 mL) to generate hydrogen sulfide in situ. Carbonyl sulfide easily undergoes hydrolysis with water to form hydrogen sulfide and carbon dioxide [11]. Reduction of the nitro group may be effected by hydrogen sulfide. When 2-nitrobenzamide was used as a starting material in the presence of carbon monoxide, sulfur, and water, 2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**1a**) was obtained under similar conditions in a reasonable yield (Equation 2).



(2)

1a 71%

Furthermore, the reaction of 2-aminobenzonitrile using water caused an addition reaction of hydrogen sulfide, generated in situ, to the cyano group to form 2-oxo-4-thio-1,2,3,4-tetrahydroquinazoline (**1g**) directly in good yield (Equation 3).



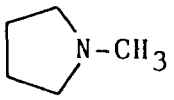
(3)

1g 90%(74%)[a]

[a] DBN was used as a base.

2,4-Dioxo-1,2,3,4-tetrahydroquinazolines (**1**) are generally available by the reaction of 2'-aminobenzamides and urea at high temperature [12]. The present sulfur-assisted carbonylation of 2-aminobenzamides with carbon monoxide may provide a useful alternative method for the synthesis of **1**.

TABLE 1 Effects of Bases and Reaction Temperature

Base	*Temp. (°C)*	*Yield (%)*[a]
DBU	80	98
	120	74
	100	85
	60	28
DBN	80	90
DABCO[b]	80	0
	80	0
Et_3N	80	0
none	80	0

[a] Isolated yields.
[b] 1,4-Diazabicyclo[2.2.2]octane.

TABLE 2 Synthesis of 2,4-Dioxo-1,2,3,4-tetrahydroquinazolines (**1a–g**)

X	*R*^{1}	*R*^{2}	*R*^{3}		*Yield (%)*[a]
O	H	H	H	**1a**	98
O	CH_3	H	H	**1b**	86
O	H	CH_3	H	**1c**	98
O	CH_3	CH_3	H	**1d**	0
O	H	H	CH_3	**1e**	97
O	H	H	Cl	**1f**	100
S	H	H	H	**1g**	99

[a] Isolated yields.

EXPERIMENTAL

IR spectra were recorded on a JASCO A-3 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a JEOL FX 90Q spectrometer using TMS as an internal standard. Mass spectra were measured with a JEOL JMS-DX-303-HF spectrometer. Melting

points were recorded with a Yanaco MICRO MELTING POINT APPARATUS or a Mettler FP 5 (uncorrected). All reactions were carried out using a 100 mL stainless steel autoclave (SUS-316) made by Taiatsu Scientific Glass Co., Ltd. The 2'-aminobenzamides, which are unavailable from commercial sources, were prepared by the esterification of the corresponding anthranilic acids with methanol followed by amidation with ammonia water (or aq methylamine). 2-Aminobenzthioamide was prepared by the reaction of 2-aminobenzonitrile with hydrogen sulfide.

Typical Procedure for The Synthesis of **1a**

Into a 100 mL stainless steel autoclave were placed 2-aminobenzamide (1.36 g, 10 mmol), powdered sulfur (30 mmol, 0.96 g), DBU (50 mmol, 7.5 mL), and THF (20 mL), and the mixture was stirred with a magnetic stirring bar under a nitrogen atmosphere. The autoclave was then flushed several times with carbon monoxide and finally charged with carbon monoxide until the pressure was 30 kg/cm^2 at room temperature. The carbonylation was carried out at 80°C for 4 h with vigorous stirring. The reaction mixture was poured into aq 1N HCl (200 mL), and a pale yellow solid was deposited. The resulting solid was washed with benzene (100 mL) and ether (50 mL) and purified by recrystallization from acetic acid to afford 2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**1a**) in 98% yield (1.59 g).

2,4-Dioxo-1,2,3,4-tetrahydroquinazoline (**1a**). Mp >300°C (>350°C [12]); IR (KBr) 3200, 3075 (N–H), 1710, 1675 cm^{-1} (C=O); ^{1}H-NMR (d$_6$-DMSO) δ = 7.08–7.36 (2H, m), 7.52–7.80 (1H, m), 7.88–8.04 (1H, m), 11.14 (1H, brs), 11.26 (1H, brs); MS (70 eV) *m/z* (rel intensity) 162 (M$^+$; 98), 119 (100), 92 (71); exact MS (70 eV) *m/z* calcd. 162.0429, obsd. 162.0419.

3-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**1b**). Mp 248°C (248–250°C [13]); IR (KBr) 3200, 3075 (N–H), 1720, 1665 cm^{-1} (C=O); ^{1}H-NMR (d$_6$-DMSO) δ = 3.20 (3H, s), 6.90–7.40 (2H, m), 7.40–8.08 (2H, m), 11.32 (1H, brs); MS (70 eV) *m/z* (rel intensity) 176 (M$^+$; 87), 119 (100); exact MS (70 eV) *m/z* calcd. 176.0586, obsd. 176.0606.

1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**1c**). Mp >300°C; IR (KBr) 3190, 3060 (N–H), 1715, 1700, 1670 cm^{-1} (C=O); ^{1}H-NMR (d$_6$-DMSO) δ = 3.84 (3H, s), 7.20–7.56 (2H, m), 7.62–8.12 (2H, m), 11.54 (1H, brs); MS (70 eV) *m/z* (rel intensity) 176 (M$^+$; 100), 105 (44), 78 (40); exact MS (70 eV) *m/z* calcd. 176.0586, obsd. 176.0600.

6-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**1e**). Mp >300°C; IR (KBr) 3180, 3060 (N–H), 1705 cm^{-1} (C=O); ^{1}H-NMR (d$_6$-DMSO) δ = 2.34 (3H, s), 7.12 (1H, d, J = 8 Hz), 7.50 (1H, d, J = 8 Hz), 7.72 (1H, s), 11.08 (1H, brs), 11.22 (1H, brs); MS (70 eV) *m/z* (rel intensity) 176 (M$^+$; 100), 133 (77); exact MS (70 eV) *m/z* calcd. 176.0586, obsd. 176.0621.

6-Chloro-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**1f**). Mp >300°C; IR (KBr) 3200, 3060 (N–H), 1705 cm^{-1} (C=O); ^{1}H-NMR (d$_6$-DMSO) δ = 7.24 (1H, d, J = 8 Hz), 7.70 (1H, d, J = 8 Hz), 7.82 (1H, s), 11.30 (1H, brs), 11.44 (1H, brs); MS (70 eV) *m/z* (rel intensity) 196 (M$^+$; 100), 153 (76), 76 (36); exact MS (70 eV) *m/z* calcd. 196.0040, obsd. 196.0047.

2-Oxo-4-thio-1,2,3,4-tetrahydroquinazoline (**1g**). Mp 271.4°C (270°C [14]); IR (KBr) 3100 (N–H), 1710 cm^{-1} (C=O); ^{1}H-NMR (d$_6$-DMSO) δ = 7.00–7.50 (2H, m), 7.50–7.96 (1H, m), 8.24–8.56 (1H, m), 11.64 (1H, brs), 12.74 (1H, brs); MS (70 eV) *m/z* (rel intensity) 178 (M$^+$; 100), 150 (21); exact MS (70 eV) *m/z* calcd. 178.0201, obsd. 178.0231.

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