Oxalyl Chloride로부터 Quinoxaline 유도체의 합성

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A Facile Entry to Quinoxalines from Oxalyl Chloride

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요 약. 출발물질인 옥살일 클로라이드를 구리-마그네슘 시약과 반응시키거나, 피롤과의 아실화 반응을 통하여 얻게 되는 1,2-케톤 화합물들을 치환된 1,2-페닐렌디아민류와 축합반응하여 여러가지 퀴녹살린 유도체를 합성하였다.

주제어: 옥살일 클로라이드, 1,2-케톤, 축합반응, 퀴녹살린

ABSTRACT. A series of quinoxalines were synthesized by the condensation between 1,2-phenylenediamines and 1,2-diketo compounds, which are available by the cross-coupling reactions of oxalyl chloride with mixed copper-magnesium reagents or by the direct acylation of pyrrole with oxalyl chloride.

Keywords: Oxalyl chloride, 1,2-Ketone, Condensation, Quinoxaline

INTRODUCTION

The quinoxaline skeleton has been used as a synthetic intermediate for the preparation of numerous compounds with interesting biological properties. Due to their conformational rigidity and their wide range of properties, such heterocyclic systems play an essential role as scaffolds in biologically active compounds. For example, they were used in the synthesis of antibacterial agents,[1a] AMPA receptor antagonists,[1b] GABA/benzodiazepine receptor agonists/antagonists,[1c] Lck inhibitors,[1d] in addition to many other pharmacologically active compounds.[2] Furthermore, the biological importance of quinoxaline-based inhibitors of receptor tyrosine kinases (RTKs) and protein kinase C (PKC) has led to a considerable amount of synthetic works in the field of such ring systems.[3]

In our efforts toward the syntheses of RTK inhibitors, a convenient synthesis of symmetrical qui-noxalines makes a problem of considerable current interest. It is reasoned that several potent RTK inhibitors commonly share the dimer-based heterocyclic framework.[3a~c,4] While there are many methods for the preparation of quinoxaline derivatives,[1~3] a facile synthesis of quinoxalines starting from oxalyl chloride would be particularly useful. Here, we would like to report a facile entry to quinoxalines from oxalyl chloride. A series of quinoxalines was easily synthesized by the condensation of 1,2-phenylenediamines with diketo compounds derived from oxalyl chloride.

RESULTS AND DISCUSSION

Cross-coupling reactions of oxalyl chloride with mixed copper-magnesium reagents. 1,2-Diones are very useful functional groups amenable to a wide variety of chemical transformations.[5] Indeed, they have been used to prepare a number of

Table 1. Reactions of oxalyl chloride with mixed copper-magnesium reagents

Entry	R[1]	Product	Yield (%)
1	3-Methoxyphenyl	1a	64
2	Benzyl	1b	73
3	Cyclohexyl	1c[a]	60
4	Cyclopentyl	1d	40
5	*n*-Pentyl	1e	58

[a]See ref. 6.

heterocyclic compounds, such as quinoxalines, dihydropyrazines, imidazoles, and pteridines. Thus, it is envisioned that a direct preparation of symmetrical diones from oxalyl chloride would offer the most concise synthetic route to the target molecule. A recent report has disclosed that cross-coupling reactions of oxalyl chloride with mixed copper-magnesium reagents in the presence of lithium bromide provide a direct access to symmetrical α-diones.[6] Thus, we carried out the cross-coupling reactions of oxalyl chloride with mixed copper-magnesium reagents derived from 3-methoxyphenyl, benzyl, cyclohexyl, cyclopentyl, and *n*-pentyl magnesium halide. The corresponding 1,2-diones 1ae were prepared in moderate yields and the results are summarized in *Table* 1.

Direct acylation of pyrrole with oxalyl chloride. Our next investigation moved to the preparation of 1,2-diones substituting heterocyclic moiety such as pyrrole, furan, and thiophene. In the literature, the preparation of 1,2-bis(1*H*-pyrrol-2-yl)ethane-1,2-dione 1f was described and refined by

Sessler.[7] The preparation involves the direct acylation of pyrrole with oxalyl chloride in the presence of pyridine at -78°C in methylene chloride as shown in Scheme 1. Instead furil 1g and 2,2-thenil 1h were commercially available. Thus, several 1,2-diones were prepared from oxalyl chloride and they were easily transformed to quinoxaline derivatives.
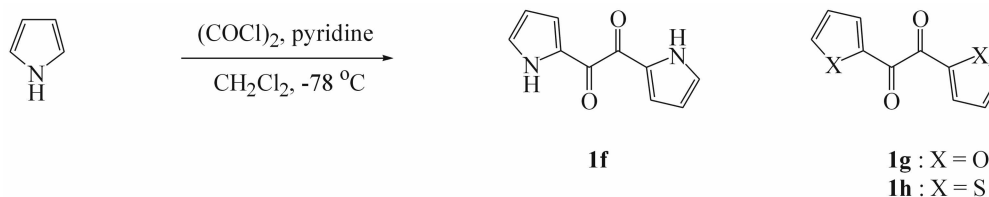
Condensation between 1,2-diones and 1,2-phenylenediamines. The subsequent condensation between 1,2-bis(3-methoxyphenyl)ethane-1,2-dione 1a with 1,2-phenylenediamine 2a in acetic acid at reflux leads to 2,3-bis(3-methoxyphenyl)quinoxaline 3a in 76% yield. Next, we extended the condensation to the readily available 3,4-diaminotoluene 2b and 4-nitro-1,2-phenylenediamine 2c leading to the quinoxalines 3b and 3c, respectively. By this procedure, a wide range of quinoxaline derivatives possessing electron-donating or -withdrawing groups, in principle, was prepared in good yield. The results on the preparations of the quinoxaline derivatives 3a-w are summarized in *Table* 2.

In summary, this study affords a facile entry to quinoxalines from oxalyl chloride. A series of quinoxalines was synthesized by the condensation between 1,2-phenylenediamines and diketo compounds, which are available by the cross-coupling reactions of oxalyl chloride with mixed copper-magnesium reagents or by the direct acylation of pyrrole with oxalyl chloride.

EXPERIMENTAL SECTION

1,2-Bis(3-methoxyphenyl)ethane-1,2-dione (1a). LiBr (3.47 g, 40 mmol) was added to the suspension of CuBr (2.93 g, 20 mol) in THF (150 mL) with stirring at room temperature under nitrogen atmosphere. After being homogeneous, the mixture

1f

1g : X = O
1h : X = S

Scheme 1.

Table 2. Quinoxaline derivatives **3a-w** prepared

1a-h + **2a** : R = H
2b : R = Me
2c : R = NO$_2$
→ AcOH reflux → **3a-w**

Entry	1,2-Dione	Phenylenediamine	Product	Yield (%)
1	1a	2a	3a	76
2	1a	2b	3b	71
3	1a	2c	3c	74
4	1b	2a	3d	83
5	1b	2b	3e	71
6	1b	2c	3f	46
7	1c	2a	3g	95
8	1c	2b	3h	78
9	1c	2c	3i	90
10	1d	2a	3j	80
11	1d	2b	3k	83
12	1e	2a	3l	96
13	1e	2b	3m	82
14	1e	2c	3n	67
15	1f	2a	3o[a]	83
16	1f	2b	3p	93
17	1f	2c	3q[a]	87
18	1g	2a	3r[b]	85
19	1g	2b	3s	85
20	1g	2c	3t	90
21	1h	2a	3u	69
22	1h	2b	3v	89
23	1h	2c	3w	78

[a]See ref. 7. [b]See ref. 3a.

was cooled to at -78°C, a 1.0 M solution of 3-methoxyphenylmagnesium bromide in THF (18 mL) and soon afterwards oxalyl chloride (1.45 g, 12 mmol) was added. The mixture was stirred for 20 min, quenched with saturated ammonium chloride solution. The solvent was removed under reduced pressure. The concentrated was partitioned with ethyl acetate and water. The organic phase was dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane=1/5, R$_f$=0.3) to give **1a** as yellowish solid (2.1 g, 64%). ^{1}H NMR (CDCl$_3$) δ 3.85 (3H, s), 3.87 (3H, s), 7.19~7.54

(8H, m); EIMS *m/z* (rel intensity) 270 (M$^-$, 22), 135 (100), 107 (25).

1,2-Dicyclopentylethane-1,2-dione (1d). ^{1}H NMR (CDCl$_3$) δ 1.60~1.86 (16H, m), 3.51~3.61 (2H, m).

Dodecane-6,7-dione (1e). ^{1}H NMR (CDCl$_3$) δ 0.89 (6H, t, *J*=7.0 Hz), 1.25~1.37 (8H, m), 1.37~1.63 (4H, m), 2.73 (4H, t, *J* = 7.4 Hz).

2,3-Bis(3-methoxyphenyl)quinoxaline (3a). The diketone **1a** (144 mg, 0.53 mmol) was dissolved in glacial acetic acid (15 mL) with stirring and to this was added a solution of 1,2-phenylenediamine (127 mg, 1.17 mmol) in acetic acid (5 mL) with stirring. The reaction mixture was then brought to reflux for

90 min under nitrogen atmosphere. After this time the majority of acetic acid was removed under vacuum and the residue was taken up with methylene chloride and water. The organic phase was washed with saturated sodium hydrogencabonate solution and water. After drying over anhydrous Na_2SO_4, the solution was filtered and evaporated to dryness. The residue obtained was then purified using silica gel column chromatography (methylene chloride, R_f = 0.45) to afford 3a as a yellowish powder (138 mg, 76%). ^{1}H NMR (CDCl$_3$) δ 3.71 (6H, s), 3.91 (2H, dd, J = 8.2, 2.4 Hz), 7.08~7.10 (2H, m), 7.22~7.26 (2H, m), 7.76~7.79 (2H, m), 8.17~8.20 (2H, m); EIMS m/z (rel intensity) 342 (M$^+$, 100), 327 (14), 311 (45), 299 (27).

2,3-Bis(3-methoxyphenyl)-6-methylquinoxaline (3b). ^{1}H NMR (CDCl$_3$) δ 2.62 (3H, s), 3.71 (6H, s), 6.90 (2H, dd, J = 8.3, 1.1 Hz), 7.06~7.08 (4H, m), 7.20~7.26 (2H, m), 7.60 (1H, dd, J = 8.6, 1.7 Hz), 7.95 (1H, s), 8.06 (1H, d, J = 8.6 Hz); EIMS m/z (rel intensity) 356 (M$^+$, 100), 325 (26), 312 (13), 180 (10).

2,3-Bis(3-methoxyphenyl)-6-nitroquinoxaline (3c). ^{1}H NMR (DMSO-d_6) δ 3.74 (6H, s), 6.99~7.34 (8H, m), 8.40 (1H, d, J = 9.1 Hz), 8.59 (1H, dd, J = 9.2, 2.5 Hz), 8.96 (1H, d, J = 2.5 Hz); EIMS m/z (rel intensity) 387 (M$^+$, 100), 372 (12), 357 (17), 356 (31), 208 (36), 164 (23).

2,3-Dibenzylquinoxaline (3d). ^{1}H NMR (CDCl$_3$) δ 4.28 (4H, s), 7.13~7.30 (10H, m), 7.29 (2H, dd, J = 6.4, 1.1 Hz), 7.82 (2H, dd, J = 6.3, 3.4 Hz); EIMS m/z (rel intensity) 310 (M$^+$, 100), 295 (13), 231 (17), 219 (43).

2,3-Dibenzyl-6-methylquinoxaline (3e). ^{1}H NMR (CDCl$_3$) δ 2.59 (3H, s), 4.25 (4H, s), 7.12~7.29 (10H, m), 7.56 (1H, dd, J = 6.1, 1.2 Hz), 7.85 (1H, s), 7.97 (1H, d, J = 6.7 Hz); EIMS m/z (rel intensity) 324 (M$^+$, 54), 309 (13), 245 (10), 233 (21), 218 (12).

2,3-Dibenzyl-6-nitroquinoxaline (3f). ^{1}H NMR (CDCl$_3$) δ 4.32 (2H, s), 4.33 (2H, s), 7.09~7.33 (10H, m), 8.19(1H, d, J = 9.1 Hz), 8.49(1H, dd, J = 8.9, 2.3 Hz), 8.98(1H, d, J = 2.4 Hz); EIMS m/z (rel intensity) 355 (M$^+$, 50), 308 (16), 218 (13), 91 (100).

2,3-Dicyclohexylquinoxaline (3g). ^{1}H NMR (CDCl$_3$) δ 1.26~1.95 (20H, m), 3.04~3.14 (2H, m), 7.26~7.64 (2H, m), 7.95~8.00 (2H, m); EIMS m/z (rel intensity) 294 (M$^+$, 87), 239 (41), 226 (66), 211 (47), 181 (41).

2,3-Dicyclohexyl-6-methylquinoxaline (3h). ^{1}H NMR (CDCl$_3$) δ 1.36~1.95 (20H, m), 2.54 (3H, s), 3.02~3.10 (2H, m), 7.45 (1H, dd, J = 8.4, 1.8 Hz), 7.76 (1H, s), 7.86(1H, d, J = 8.4 Hz); EIMS m/z (rel intensity) 308 (M$^+$, 100), 253 (57), 240 (68), 225 (38).

2,3-Dicyclohexyl-6-nitroquinoxaline (3i). ^{1}H NMR (CDCl$_3$) δ 1.26~1.97 (20H, m), 3.08~3.16 (2H, m), 8.09 (1H, d, J = 9.3 Hz), 8.40 (1H, dd, J = 9.0, 2.4 Hz), 8.90 (1H, d, J = 2.4 Hz); EIMS m/z (rel intensity) 339 (M$^+$, 80), 284 (54), 271 (100), 256 (47).

2,3-Dicyclopenylquinoxaline (3j). ^{1}H NMR (CDCl$_3$) δ 1.72~2.09 (16H, m), 3.59~3.70 (2H, m), 7.58~7.63 (2H, m), 7.93~7.99 (2H, m); EIMS m/z (rel intensity) 266 (M$^+$, 71), 225 (100).

2,3-Dicyclopentyl-6-methylquinoxaline (3k). ^{1}H NMR (CDCl$_3$) δ 1.72~2.08 (16H, m), 2.54 (3H, s), 3.59~3.65 (2H, m), 7.44 (1H, dd, J = 8.4, 1.8 Hz), 7.75 (1H, s), 7.84 (1H, d, J = 8.4 Hz); EIMS m/z (rel intensity) 280 (M$^+$, 39), 251 (4), 239 (25), 223 (4), 209 (11), 195 (17), 183 (16).

2,3-Dipenylquinoxaline (3l). ^{1}H NMR (CDCl$_3$) δ 0.93 (6H, t, J = 6.9 Hz), 1.37~1.51 (8H, m), 1.78~1.89 (4H, m), 3.00 (4H, t, J = 8.1 Hz), 7.62~7.68 (2H, m), 7.97~8.02 (2H, m); EIMS m/z (rel intensity) 270 (M$^+$, 5), 214 (100), 199 (46), 185 (70), 169 (21), 157 (47).

6-Methyl-2,3-dipentylquinoxaline (3m). ^{1}H NMR (CDCl$_3$) δ 0.93 (6H, t, J = 6.8 Hz), 1.37~1.51 (8H, m), 1.77~1.87 (4H, m), 2.55 (3H, s), 2.98 (4H, t, J = 8.2 Hz), 7.47 (1H, dd, J = 7.8, 1.4 Hz), 7.77 (1H, s), 7.88 (1H, d, J = 8.0 Hz); EIMS m/z (rel intensity) 284 (M$^+$, 8), 228 (100), 213 (41), 199 (75), 185 (47), 172 (78).

6-Nitro-2,3-dipentylquinoxaline (3n). ^{1}H NMR (CDCl$_3$) δ 0.95 (6H, t, J = 7.2 Hz), 1.43~1.49 (8H, m), 1.80~1.87 (4H, m), 3.04 (4H, t, J = 7.8 Hz), 8.11 (1H, d, J = 9.0 Hz), 8.43 (1H, dd, J = 9.0, 2.4 Hz), 8.92 (1H, d, J = 2.4 Hz); EIMS m/z (rel intensity) 315 (M$^+$, 5), 259 (100), 244 (25), 230 (43).

6-Methyl-2,3-bis(1*H*-pyrrol-2-yl)quinoxaline (3p). ^{1}H NMR (CDCl$_3$) δ 2.51 (3H, s), 6.25~6.28 (2H, m), 6.87~6.97 (4H, m), 7.38 (1H, dd, *J* = 8.4, 1.8 Hz), 7.64 (1H, s), 7.76 (1H, d, *J* = 8.4 Hz), 9.59 (2H, d, *J* = 12.6 Hz); EIMS *m/z* (rel intensity) 274 (M⁺, 100), 258 (100), 243 (62), 218 (24).

2,3-Di(furan-2-yl)-6-methylquinoxaline (3s). ^{1}H NMR (CDCl$_3$) δ 2.60 (3H, s), 6.55~6.57 (2H, dd, *J* = 3.3, 1.6 Hz), 6.63 (2H, d, *J* = 3.5 Hz), 7.57~7.62 (3H, m), 7.92 (1H, s), 8.03 (1H, d, *J* = 8.6 Hz); EIMS *m/z* (rel intensity) 276 (M⁺, 100), 259 (45), 247 (42), 219 (40).

2,3-Di(furan-2-yl)-6-nitroquinoxaline (3t). ^{1}H NMR (CDCl$_3$) δ 6.61~6.64 (2H, m), 6.86 (2H, dd, *J* = 16.8, 3.6 Hz), 7.67~7.69 (2H, m), 8.23 (1H, d, *J* = 9.2 Hz), 8.49 (1H, dd, *J* = 9.3, 2.7 Hz), 9.01 (1H, d, *J* = 2.4 Hz); EIMS *m/z* (rel intensity) 307 (M⁺, 100), 290 (30), 233 (28), 168 (34).

2,3-Di(thiophen-2-yl)quinoxaline (3u). ^{1}H NMR (CDCl$_3$) δ 7.04 (2H, m), 7.24 (2H, m), 7.50 (2H, d, *J* = 5.0 Hz), 7.71~7.74 (2H, m), 8.05~8.10 (2H, m); EIMS *m/z* (rel intensity) 294 (M⁺, 100), 261 (16), 185 (20).

6-Methyl-2,3-di(thiophen-2-yl)quinoxaline (3v). ^{1}H NMR (CDCl$_3$) δ 2.57 (3H, s), 7.01~7.04 (2H, m), 7.20~7.23 (2H, m), 7.47 (2H, m), 7.55 (1H, d, *J* = 1.8 Hz), 7.84 (1H, s), 7.95 (1H, d, *J* = 8.3 Hz); EIMS *m/z* (rel intensity) 308 (M⁺, 10), 275 (8), 198 (23).

6-Nitro-2,3-di(thiophen-2-yl)quinoxaline (3w). ^{1}H NMR (DMSO-*d$_6$*) δ 7.13~7.18 (2H, m), 7.36 (2H, dd, *J* = 12.0, 3.7 Hz), 7.90 (2H, m), 8.24 (1H, d, *J* = 9.1 Hz), 8.47 (1H, dd, *J* = 9.2, 2.4 Hz), 8.79 (1H, d, *J* = 2.1 Hz); EIMS *m/z* (rel intensity) 337 (M⁺, 100), 309 (10), 293 (17), 260 (9), 230 (12), 215 (8).

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