Heterocyclic Compounds with Sulfone Functional Groups (II) : Synthesis of 1-Arenesulfonyl-2-quinoxalinones

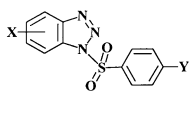
Young-Seuk Hong,* Hyun-Muk Kim, Yong-Tae Park,† and Ho-Sik Kim‡

Department of Chemistry, Keimyung University, Daegu 704-701, Korea
†Department of Chemistry, Kyungpook National University, Daegu 702-701, Korea
‡Department of Chemistry, Catholic Univ. of Taegu-Hyosung, Gyongsan 713-702, Korea
Received August 19, 1999

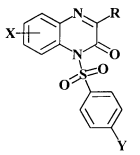
During last few decades many quinoxaline derivatives have been synthesized for biological, medical and industrial purposes. For examples, 1,2-dihydro-1-polyhydroxyalkyl-quinoxalin-2-ones for anti-inflammation,[1] 2-alkoxyquinoxalinylphosphorothioates for insecticide,[2] quinoxaline acetophenone oximes for treatment of hypertension[3] and 2-acetyl-3-(methylsulfonyl)methyl-quinoxaline-1-oxide for antibiosis.[4] There are, however, not any reports on synthesis of 1-arenesulfonyl derivatives of 2(1*H*)-quinoxalinones and on their biological activities.

On the other hand, during last decade, many benzotriazol-1-yl derivatives were synthesized by A. Katritzky and others for biological activities,[5] industrial purpose[6] and simply synthetic interest.[7] They reported that benzotriazol-1-yl (Bt-1-yl) group acts as same manner as halogen atoms,[8] although the compounds with Bt-1-yl group is more stable than those with halogen atoms. And they have also synthesized some 1-arenesulfonylbenzotriazoles **1**.[9] Because it seems that 2-quinoxalinon-1-yl group has chemically a similar property to Bt-1-yl group, so it is expected that 1-arenesulfonyl-2-quinoxalinones have the biological activities and the sulfonation on 1-position of the corresponding compounds is relatively easy.

This study deals with synthetic methods of some 1-arenesulfonyl-2-quinoxalinones **2**, which are valuable to be scrutinized on their biological activities.



X = H, Me, NO_2, Cl
Y = H, Me
1



X = H, Me, NO_2, Cl
R and Y = H, Me
2

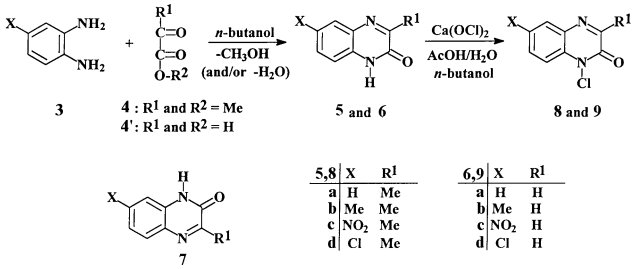
Results and Discussion

6-Substituted 3-methyl-2(1*H*)-quinoxalinones 5a-d.[10] 6-Substituted 3-methyl-2(1*H*)-quinoxalinones **5a-d** were prepared by the reactions of the corresponding *o*-phenylenediamines **3** and methyl pyruvate **4**[10] (Scheme 1). The yields of the products **5a-d** were in the range of 76-89%. Bakerman suggested the mechanism,[11] in which two amino groups of **3** stepwisely attack two carbonyl centers of **4** (first to the carbonyl carbon), followed by eliminating of a water and a methanol molecule. However, there is theoretically a possibility to give the compounds **7** by different attacking orientation of *o*-phenylenediamines **3** with a substituent such as methyl, chloro and nitro group in the phenyl ring. But we couldn't isolate the compound **7** from the reaction solutions, which means that the *m*-amino group of compounds **3** is more powerful to attack the carbonyl carbon center nucleophilically than *p*-amino group of **3** is. On the other hand, it was checked by ^{1}H NMR and IR spectra that the compounds **5** existed only as *oxo*-tautomer, not *hydroxy*-form.

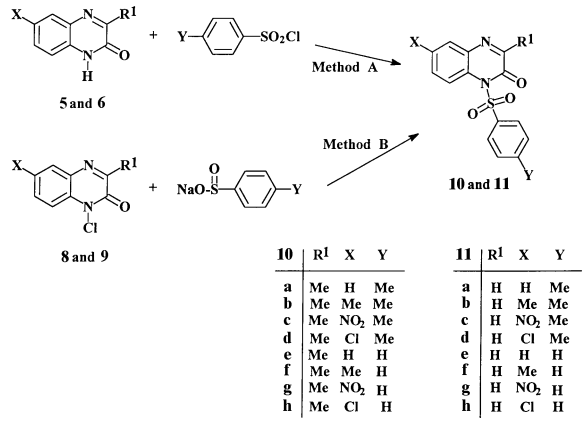
6-Substituted 2(1*H*)-quinoxalinones 6a-d. Compounds **6a-d** were prepared by the reactions of corresponding **3** and glyoxylic acid **4'** (Scheme 1), which is also expected to proceed by nucleophilic addition of two amino groups stepwisely and elimination of two water molecules. It was checked by ^{1}H NMR and IR spectra that the compounds **6** existed as *oxo*-tautomer too. The yields of the products **6a-d** were in the range of 51-82%.

6-Substituted 1-chloro-2-quinoxalinones derivatives 8a-d and 9a-d. The reactions of **5** and **6** with calcium hypochlorite gave 1-chloro-3-methyl-2-quinoxalinones **8** and 1-chloro-2-quinoxalinones **9** respectively (Scheme 1). The products were identified by elementary analysis, IR spectra in which NH stretching bands near 3320 cm^{-1} were disappeared and ^{1}H NMR spectra in which peaks near 12.5 ppm of **5** and **6** were gone too. The yields of products **8a-d** and **9a-d** were in the ranges of 67-87% and 80-92%, respectively.

1-Arenesulfonyl-2-quinoxalinones 11a-h and their 3-methyl derivatives 10a-h. We used two methods to synthesize compounds **10** and **11**. The one (method A) was by the electrophilic substitution of arenesulfonyl chlorides ($ArSO_2Cl$) to the compounds **5** and **6** respectively, and the other (method B) was by the nucleophilic substitution of sodium



Scheme 1



10	R^1	X	Y
a	Me	H	Me
b	Me	Me	Me
c	Me	NO_2	Me
d	Me	Cl	Me
e	Me	H	H
f	Me	Me	H
g	Me	NO_2	H
h	Me	Cl	H

11	R^1	X	Y
a	H	H	Me
b	H	Me	Me
c	H	NO_2	Me
d	H	Cl	Me
e	H	H	H
f	H	Me	H
g	H	NO_2	H
h	H	Cl	H

Scheme 2

arenesulfinates (NaOS(=O)Ar) to the compounds **8** and **9** respectively. The yields of products **10a-h** prepared by method A were in the range of 61-74% and by method B 49-69% respectively, and the yields of products **11a-h** prepared by method A were in the range of 58-76% and by method B 32-75%. The one-step reactions from the quinoxalinones **5** and **6** (method A) gave rather good yields than the two-step reactions *via* 1-chloro derivatives **8** and **9** (method B) did.

Experimental Section

Apparatus for identification of compounds. ^{1}H NMR spectra were taken on Bruker AVANCE 400, and chemical shifts given in ppm downfield from TMS as internal standard. IR spectra were taken on Mattson Research II Model. And melting points were determined on Melting Point Apparatus (Jencons 9200) and are uncorrected.

3-Methyl-2(1*H*)-quinoxalinones 5a-d. A mixed solution of *o*-phenylenediamine **3a** (2.0 g, 18.5 mmol) and methyl pyruvate **4a** (2.26 g, 22.2 mmol) in *n*-butanol (60 mL) was refluxed for 2 hrs in boiling water bath. After standing at room temperature for a while, the solid formed was filtered under reduced pressure and washed with *n*-hexane (20 mL) to give light-yellow crystal of 3-methyl-2(1*H*)-quinoxalinone **5a** (2.64 g, yield 89%; mp 247-248 °C). 3,6-Dimethyl-2(1*H*)-quinoxalinone **5b** (2.45 g, yield 76%; mp 204-206 °C), 3-methyl-6-nitro-2(1*H*)-quinoxalinone **5c** (3.34 g, yield 88%; mp 229-230 °C), and 3-methyl-6-chloro-2(1*H*)-quinoxalinone **5d** (3.10 g, yield 86%; mp 246-247 °C) were prepared by similar procedure to the preparation of **5a**. All products were recrystallized from a mixed solvent of DMF and ethanol (vol. 3 : 7). The ^{1}H NMR and IR spectral data of the products **5a-d** are shown in Table 1.

2(1*H*)-Quinoxalinones 6a-d. A mixed solution of *o*-phenylenediamine **3a** (4.32 g, 40 mmol) and glyoxylic acid **4'a** (4.6 g, 50 mmol) in *n*-butanol (120 mL) was refluxed for 5 hrs. After standing in a freezer for one night, the solid formed was filtered under reduced pressure and washed with *n*-hexane (20 mL) to give light-yellow crystal of 2(1*H*)-quinoxalinone **6a** (4.56 g, yield 78%; mp 236-237 °C). 6-Methyl-2(1*H*)-quinoxalinone **6b** (3.24 g, yield 51%; mp 196-197 °C), 6-nitro-2(1*H*)-quinoxalinone **6c** (6.26 g, yield 82%; mp 224-226 °C), and 6-chloro-2(1*H*)-quinoxalinone **6d** (5.58 g, yield 77%; mp 239-241 °C) were prepared by similar procedure to the preparing of **6a**. All products were recrystallized in a mixed solvent of DMF and ethanol (vol. 3 : 7). The ^{1}H NMR and IR spectral data of the products **6a-d** are shown in Table 1.

1-Chloro-3-methyl-2-quinoxalinones 8a-d. The compound **5a** (1.6 g, 10 mmol) was dissolved in a mixed solvent (20 mL) of acetic acid and water (vol. 1 : 1), and *n*-butanol (50 mL). To this solution, calcium hypochlorite solution (20 mmol) in acetic acid and water (15 mL, vol. 1 : 5) was added dropwise, and stirred for 4 hrs. After the solid formed was filtered under reduced pressure and washed with 50 mL of water 3 times to give the reddish-brown crystal of 1-chloro-3-methyl-2-quinoxalinone **8a** (1.3 g, yield 67%; mp 243-245 °C). 1-Chloro-3,6-dimethyl-2-quinoxalinone **8b** (1.66 g, yield 80%; mp 162-164 °C), 1-chloro-3-methyl-6-nitro-2-quinoxalinone **8c** (1.81 g, yield 75%; mp 321-322 °C), and 1,6-dichloro-3-methyl-2-quinoxalinone **8d** (1.99 g, yield 87%; mp 234-235 °C) were prepared by similar procedure to the preparation of **8a**. All products were recrystallized from a mixed solvent of DMF and ethanol (vol. 3 : 7). The ^{1}H NMR and IR spectral data of the products **8a-d** are shown in Table 1.

1-Chloro-2-quinoxalinones 9a-d. The compound **6a** (1.02 g, 7 mmol) was dissolved in a mixed solvent (10 mL) of acetic acid and water (vol. 1 : 1). To this solution, calcium hypochlorite solution (20 mmol) in acetic acid and water (45 mL, vol. 1 : 5) was dropwisely added, and stirred for 12 hrs. The solid formed in the reaction mixture was filtered under reduced pressure and washed with water and *n*-hexane (20 mL) to give the reddish-brown crystal of 1-chloro-2-quinoxalinone **9a** (1.44 g, yield 80%; mp 228-230 °C). 1-Chloro-6-methyl-2-quinoxalinone **9b** (1.67 g, yield 86%; mp 225-227 °C), 1-chloro-6-nitro-2-quinoxalinone **9c** (1.93 g, yield 86%; mp 216-217 °C), and 1,6-dichloro-2-quinoxalinone **9d** (1.98 g, yield 92%; mp 233-235 °C) were prepared by similar procedure to the preparation of **9a**. All products were recrystallized from a mixed solvent of DMF and ethanol (vol. 3 :7). The ^{1}H NMR and IR spectral data of the products **9a-d** are shown in Table 1.

1-Arenesulfonyl-3-methyl-2-quinoxalinones 10a-h. Method A. To mixture of **5a** (1.6 g, 10 mmol) and potassium hydroxide (0.84 g, 15 mmol) dissolved in DMSO (30 mL), the solution of *p*-toluenesulfonyl chloride (1.91 g, 10 mmol) in DMSO (15 mL) was dropwisely added. The solution was stirred and heated at 130 °C for 30 hrs. After the solution was poured into water (200 mL), the solid formed was filtered under reduced pressure, and washed with water (50 mL × 3) and *n*-hexane (15 mL) to give dark-brown crystal of 1-toluenesulfonyl-3-methyl-2-quinoxalinone **10a** (2.11 g, yield 67%; mp 229-230 °C). 1-Toluenesulfonyl-3,6-dimethyl-2-quinoxalinone **10b** (2.0 g, yield 61%; mp 307-309 °C), 1-toluenesulfonyl-3-methyl-6-nitro-2-quinoxalinone **10c** (2.66 g, yield 74%; mp 300-301 °C), and 1-toluenesulfonyl-3-methyl-6-chloro-2-quinoxalinone **10d** (2.44 g, yield 70%; mp 319-320 °C) were prepared by similar procedure to

Table 1. Spectral data of 2(1*H*)-quionxalinone derivatives

product	^{1}H NMR (DMSO-d$_6$), ppm	IR (KBr, cm^{-1})
5a	12.31 (br, 1H, N*H*), 7.69 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.47 (t, *J* = 6.8 Hz, 1H, Ar-*H*), 7.29 (m, 2H, Ar-*H*), 2.42 (s, 3H, C*H*$_3$)	3308 (NH), 1669 (C=O)
5b	12.23 (br, 1H, N*H*), 7.58-7.05 (m, 3H, Ar-*H*), 2.39 (s, 3H, C*H*$_3$), 2.37 (s, 3H, C*H*$_3$)	3312 (NH), 1667 (C=O)
5c	12.73 (br, 1H, N*H*), 8.41-7.37 (m, 3H, Ar-*H*), 2.44 (s, 3H, C*H*$_3$)	3323 (NH), 1682 (C=O), 1539 (C-NO$_2$), 1343 (C-NO$_2$)
5d	12.37 (br, 1H, N*H*), 7.71-7.25 (m, 3H, Ar-*H*), 2.40 (d, *J* = 6.4 Hz, 3H, C*H*$_3$)	3306 (NH), 1669 (C=O)
6a	12.45 (br, 1H, N*H*), 8.18 (s, 1H, C$_3$-*H*), 7.80-7.30 (m, 4H, Ar-*H*)	3298 (NH), 1680 (C=O)
6b	12.37 (br, 1H, N*H*), 8.12 (d, *J*=20 Hz, 1H, C$_3$-*H*), 7.67-7.09 (m, 3H, Ar-*H*), 2.39 (d, *J* = 12 Hz, 3H, C*H*$_3$)	3299 (NH), 1688 (C=O)
6c	12.76 (br, 1H, N*H*), 8.75-8.10 (m, 4H, Ar-*H*)	3329 (NH), 1678 (C=O), 1520 (C-NO$_2$), 1352 (C-NO$_2$)
6d	12.55 (br, 1H, N*H*), 8.20 (s, 1H, C$_3$-*H*), 7.85-7.30 (m, 3H, Ar-*H*)	3300 (NH), 1692 (C=O)
8a	7.71-7.24 (m, 4H, Ar-*H*), 2.42 (s, 3H, C*H*$_3$)	1669 (C=O)
8b	7.74-6.94 (m, 3H, Ar-*H*), 2.44 (s, 3H, C*H*$_3$), 2.41 (s, 3H, C*H*$_3$)	1653 (C=O)
8c	8.43-7.39 (m, 3H, Ar-*H*), 2.44 (s, 3H, C*H*$_3$)	1683 (C=O), 1540 (C-NO$_2$), 1340 (C-NO$_2$)
8d	7.72-7.26 (m, 3H, Ar-*H*), 2.40 (s, 3H, C*H*$_3$)	1699 (C=O), 1489
9a	8.18 (s, 1H, C$_3$-*H*), 7.80-7.30 (m, 4H, Ar-*H*)	1684 (C=O)
9b	8.13 (d, *J*=20.8 Hz, 1H, C$_3$-*H*), 7.67-7.09 (m, 3H, Ar-*H*), 2.39 (d, *J*=10 Hz, 3H, C*H*$_3$)	1682 (C=O)
9c	8.59-7.47 (m, 4H, Ar-*H*)	1680 (C=O), 1523 (C-NO$_2$), 1358 (C-NO$_2$)
9d	8.22 (s, 1H, C$_3$-*H*), 7.85-7.31 (m, 3H, Ar-*H*)	1690 (C=O)
10a	7.77-7.12 (m, 8H, Ar-*H*), 2.40 (s, 3H, C*H*$_3$), 2.37 (s, 3H, C*H*$_3$)	1669 (C=O), 1176 (N-SO$_2$-)
10b	7.91-7.06 (m, 7H, Ar-*H*), 2.50 (s, 3H, C*H*$_3$), 2.41 (s, 3H, C*H*$_3$), 2.35 (s, 3H, C*H*$_3$)[a]	1669 (C=O), 1187 (N-SO$_2$-)
10c	8.45-7.40 (m, 7H, Ar-*H*), 2.50 (s, 3H, C*H*$_3$), 2.43 (s, 3H, C*H*$_3$)[a]	1698 (C=O), 1540 (C-NO$_2$), 1340 (C-NO$_2$), 1184 (N-SO$_2$-)
10d	7.96-7.12 (m, 7H, Ar-*H*), 2.89 (s, 3H, C*H*$_3$), 2.73 (s, 3H, C*H*$_3$)	1683 (C=O), 1178 (N-SO$_2$-)
10e	7.93-6.72 (m, 9H, Ar-*H*), 2.50 (s, 3H, C*H*$_3$)[a]	1669 (C=O), 1182 (N-SO$_2$-)
10f	7.95-6.64(m, 8H, Ar-*H*), 2.89 (s, 3H, C*H*$_3$), 2.73 (s, 3H, C*H*$_3$)	1669 (C=O), 1190 (N-SO$_2$-)
10g	8.49-7.06 (m, 8H, Ar-*H*), 2.50 (s, 3H, C*H*$_3$)[a]	1698 (C=O), 1522 (C-NO$_2$), 1341 (C-NO$_2$), 1178 (N-SO$_2$-)
10h	7.87-6.62 (m, 8H, Ar-*H*), 2.51 (s, 3H, C*H*$_3$)	1669 (C=O)
11a	8.17-7.29 (m, 9H, Ar-*H*), 2.09 (s, 3H, C*H*$_3$)	1689 (C=O), 1144 (N-SO$_2$-)
11b	8.15-7.09 (m, 8H, Ar-*H*), 2.41 (s, 3H, C*H*$_3$), 2.38 (s, 3H, C*H*$_3$)	1689 (C=O), 1140 (N-SO$_2$-)
11c	8.55 (s, 1H, C$_3$-*H*), 8.40-7.06 (m, 7H, Ar-*H*), 2.51 (d, *J*=9.2 Hz, 3H, C*H*$_3$)	1678 (C=O), 1529 (C-NO$_2$), 1342 (C-NO$_2$)
11d	8.22-7.31 (m, 8H, Ar-*H*), 2.09 (s, 3H, C*H*$_3$)	1690 (C=O), 1184 (N-SO$_2$-)
11e	8.18-7.29 (m, 10H, Ar-*H*)	1679 (C=O), 1143 (N-SO$_2$-)
11f	7.96-6.88 (m, 9H, Ar-*H*), 2.50 (s, 3H, C*H*$_3$)[a]	1678 (C=O), 1125 (N-SO$_2$-)
11g	8.46-7.88 (m, 9H, Ar-*H*)	1679 (C=O), 1584 (C-NO$_2$), 1333 (C-NO$_2$)
11h	7.97-7.15 (m, 9H, Ar-*H*)	1688 (C=O), 1127 (N-SO$_2$-)

[a]solvent $CDCl_3$

the preparation of **10a**. Compounds **10e-h** were also synthesized by the reactions of the corresponding **5** and sodium benzenesulfinate. 1-Benzenesulfonyl-3-methyl-2-quinoxalinone **10e** (2.2 g, yield 73%; mp 304-306 °C), 1-benzenesulfonyl-3,6-dimethyl-2-quinoxalinone **10f** (2.29 g, yield 73%; mp 354-355 °C), 1-benzenesulfonyl-3-methyl-6-nitro-2-quinoxalinone **10g** (2.56 g, yield 74%; mp 208-209 °C), and 1-benzenesulfonyl-3-methyl-6-chloro-2-quinoxalinone **10h** (2.41 g, yield 72%; mp 236-238 °C) were prepared by similar procedure to the preparation of **10a**.

Method B. A mixed solution of **8a** (5.84 g, 30 mmol) and sodium *p*-toluenesulfinate (5.35 g, 30 mmol) in DMSO (30 mL) was refluxed for 24 hrs, and the reaction solution was poured into water (200 mL). The solid formed was filtered under reduced pressure and washed with water (50 mL × 3) and *n*-hexane (15 mL) to give dark-brown crystal of **10a** (4.71 g, yield 50%). **10b** (4.82 g, yield 49%), **10c** (5.39 g, yield 50%), and **10d** (5.75 g, yield 55%) were prepared by similar procedure to the preparation of **10a**. Compounds **10e-h** were also synthesized by the reactions of the corresponding **8** and sodium benzenesulfinate. **10e** (4.86 g, yield 54%), **10f** (6.03 g, yield 64%), **10g** (6.62 g, yield 65%), and **10h** (6.93 g, yield 69%) were prepared by similar procedure to the preparation of **10a** (method B). All products were recrystallized from a mixed solvent of DMF and ethanol (vol. 3 : 7). The ^{1}H NMR and IR spectral data of the products **10a-h** are shown in Table 1.

1-Arenesulfonyl-2-quinoxalinones 11a-h. Method A. To a mixture of **6a** (2.92 g, 20 mmol) and potassium hydroxide (1.68 g, 30 mmol) dissolved in DMSO (50 mL), the solution of *p*-toluenesulfonyl chloride (3.81 g, 20 mmol) in DMSO (15 mL) was dropwisely added. The solution was stirred and heated at 130 °C for 24 hrs. After the solution was poured into water (200 mL), the solid formed was filtered under

reduced pressure, and washed with water (50 mL × 3) and *n*-hexane (30 mL) to give reddish-brown crystal of 1-toluenesulfonyl-2-quinoxalinone **11a** (3.70 g, yield 61%; mp 202-204 °C). 1-Toluenesulfonyl-6-methyl-2-quinoxalinone **11b** (3.64 g, yield 58%; mp 257-259 °C), 1-toluenesulfonyl-6-nitro-2-quinoxalinone **11c** (5.25 g, yield 76%; mp 250-251 °C), and 1-toluenesulfonyl-6-chloro-2-quinoxalinone **11d** (4.69 g, yield 70%; mp 269-270 °C) were prepared by similar procedure to the preparation of **11a**. Compounds **11e-h** were also synthesized by the reactions of the corresponding **6** and sodium benzenesulfinate. 1-Benzenesulfonyl-2-quinoxalinone **11e** (3.38 g, yield 59%; mp 254-256 °C), 1-benzenesulfonyl-6-methyl-2-quinoxalinone **11f** (3.60 g, yield 60%; mp 278-279 °C), 1-benzenesulfonyl-6-nitro-2-quinoxalinone **11g** (4.70 g, yield 71%; mp 181-182 °C), and 1-benzenesulfonyl-6-chloro-2-quinoxalinone **11h** (4.30 g, yield 67%; mp 216-217 °C) were prepared by similar procedure to the preparation of **11a**. All products were recrystallized from a mixed solvent of DMF and ethanol (vol. 3 : 7).

Method B. A mixed solution of **9a** (0.90 g, 5 mmol) and sodium *p*-toluenesulfinate (0.89 g, 5 mmol) in DMF (30 mL) and dioxane (10 mL) was refluxed for 24 hrs. The solvent was removed under reduced pressure, the solid formed was washed with water (50 mL × 3) and *n*-hexane (20 mL) to give reddish-brown crystal of **11a** (0.48 g, yield 32%). **11b** (0.94 g, yield 60%), **11c** (1.19 g, yield 69%), and **11d** (1.26 g, yield 75%) were prepared by similar procedure to the preparation of **11a**. Compounds **11e-h** were also synthesized by reactions of **9** and sodium benzenesulfinate. **11e** (0.86 g, yield 60%), **11f** (0.87 g, yield 58%), **11g** (1.14 g, yield 69%), and **11h** (1.19 g, yield 74%) were prepared by similar procedure to the preparation of **11a** (method B). All products were recrystallized in a mixed solvent of DMF and ethanol. The ^{1}H NMR and IR spectral data of the products **11a-h** are shown in Table 1.

Acknowledgment. It is gratefully acknowledged that this work was in part supported by Bisa Research Fund of Keimyung University (1998) and by the Basic Science Research Program, Ministry of Education, Korea (BSRI-97-3402).

References

1. Wendt, G. R.; Ledig, K. W. *U. S. Pat.* **1969**, 3,431,262 (*Chem. Abstr.*, **1969**, *70*, 106,512).
2. Magee, R. J. *U. S. Pat.* **1972**, 3,634,425 (*Chem. Abstr.*, **1972**, *76*, 99,709S).
3. (a) Kumade, S.; Watanabe, N.; Yamamoto, K.; Zenno, H. *Yakugaku Zasshi* **1958**, *30*, 635. (b) Monge, A.; Palop, J. A.; Fernandez, E. *J. Heterocyclic Chem.* **1989**, *26*, 1623.
4. (a) Tanaka, A.; Usui, T. *Chem. Pharm., Bull.* **1981**, *29*, 110. (b) Awad, I. M. A. *Ind. J. Chem.* **1991**, *30B*, 89.
5. (a) Lalezari, I.; Gomez, L. A.; Khorshidi, M. *J. Heterocycl. Chem.* **1990**, *27*, 687. (b) Bochis, R. J. *J. Med. Chem.* **1991**, *34*, 2843. (c) Caliendo, G.; Novellino, E.; Sagliocco, G.; Santagada, V. E. *J. Med. Chem.* **1992**, *27*, 161. (d) Caliendo, G.; Carlo, R.; Meli, R.; Perissutti, E. *J. Med. Chem.* **1993**, *28*, 969.
6. (a) Brizzi, V.; Franchi, G.; Savini, L. *Boll. Chim. Pharmacol.* **1986**, *125*, 100. (b) Poskocil, J.; Hirsch, K.; Adamek, M.; Korinek, J. *Chem. Prum.* **1982**, *32*, 300. (c) Huston, A. L.; Scott, G. W. *J. Phys. Chem.* **1987**, *91*, 1408. (d) Li, S.; Gupta, A.; Albertsson, A. C.; Bassett, W.; Vogl, O. *Polym. Bull.* **1984**, *12*, 237. (e) Vogl, O.; Albertsson, A. C.; Janovic, Z. *Polymer* **1985**, *26*, 1288.
7. (a) Berti, C.; Greci, L.; Andruzzi, R.; Trazza, A. *J. Org. Chem.* **1982**, *47*, 4895. (b) Rigby, J. H.; Holswort, D. D.; James, K. *J. Org. Chem.* **1989**, *54*, 4019. (c) Whitney, S. E.; Winters, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 929. (d) Hoeg-Jensen, T.; Olsen, C. E.; Holm, A. *J. Org. Chem.* **1994**, *59*, 1257.
8. (a) Makino, K.; Yoshioka, H. *Heterocycles* **1987**, *26*, 1215. (b) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683. (c) Katritzky, A. R.; Fan, Q. W. *J. Fluorine Chem.* **1991**, *51*, 33.
9. (a) Beveridge, S.; Huppstz, J. L. *Aust. J. Chem.* **1972**, *25*, 1341. (b) Katritzky, A. R.; Shobana, N.; Afridi, A. S. *Tetrahedron* **1992**, *48*, 7817. (c) Katritzky, A. R.; Fan, Q. W.; Steel, P. J. *J. Org. Chem.* **1992**, *57*, 190.
10. (a) L'Italien, J.; Banks, C. K. *J. Am. Chem. Soc.* **1951**, *73*, 3246. (b) Leese, C. L.; Rydon, H. N. *J. Chem. Soc.* **1955**, 303.
11. Bakerman, D. G.; Abasolo, M. I.; Fernandez, B. M. *J. Heterocyclic Chem.* **1992**, *29*, 129.