REACTION OF BENZAMIDE OXIME DERIVATIVES WITH CHLOROCARBONYLSULFENYL CHLORIDE[1]

Etsuko Kawashima, Yuko Ando, Toyozo Takada, and Katsumi Tabei*
Department of Organic Chemistry, Tokyo College of Pharmacy
1432-1 Horinouchi, Hachioji City, Tokyo 192-03, Japan

Abstract — Benzamide oxime derivatives (**1**) were reacted with chlorocarbonylsulfenyl chloride (**2**) in the presence of a base as a catalyst to afford 3-aryl-4,5-dihydro-1,2,4-thiadiazol-5-one (**3**), 3-aryl-4,5-dihydro-1,2,4-oxadiazol-5-one (**4**) and di(benzamide) O,O'-carboxime (**5**) derivatives in moderate yields. The reaction of N-ethyl-p-toluamide oxime (**7**) with **2** gave 4-ethyl-4,5-dihydro-3-(p-tolyl)-1,2,4-thiadiazol-5-one (**8**) and 4-ethyl-4,5-dihydro-3-(p-tolyl)-1,2,4-oxadiazol-5-one (**9**).

Chlorocarbonylsulfenyl chloride (CCSC) has at least two reaction sites, carbonyl chloride and sulfenyl chloride groups in its structure. It is widely used for the synthesis of S-heterocyclic compounds.[2] Our attention has been directed to a reaction of amide oxime derivatives with CCSC for the syntheses of thiadiazoles and oxadiazoles. The results and possible mechanisms are discussed in detail in the following.

p-Toluamide oxime (**1a**) was treated with an equimolar amount of CCSC (**2**) in dry acetonitrile in the presence of triethylamine at 0°C to afford a pale brown tarry substance. On subjecting it to a chromatographic workup, colorless needles of mp 218°C, $C_9H_8N_2OS$ (**3a**), colorless needles of mp 223°C, $C_9H_8N_2O_2$ (**4a**), and colorless prisms of mp 145°C, $C_{17}H_{18}N_4O_3$ (**5a**) were obtained in 13, 16 and 3.0% yield, respectively. When the reaction mixture was heated at reflux, the yields of **3a** and **4a** were somewhat better, being 17 and 21%, respectively. p-Tolylurea (**6a**), mp 184°C, was also obtained in 3.0% yield.

However, product **5a** could not be isolated, and **5a** was only detected by TLC.

An appreciable amount of sulfur was obtained from the first elution under the above reaction conditions.

The structure of **3a** was assigned to 4,5-dihydro-3-(p-tolyl)-1,2,4-thiadiazol-5-one from the following analytical and spectral data. The mass spectrum of **3a** showed its molecular ion peak at m/z 192 and the base peak at m/z 149 which was assigned to CH_3-C_6H_4-CNS^+ ion.

Characteristic absorption bands of **3a** appeared at 3150 (NH), 1660 (C=O) and 1640 (C=N) cm^{-1}, respectively. In the ^{1}H-nmr spectrum of **3a**, characteristic signals due to NH, tolyl-methyl and the aromatic ring appeared at 11.1 (1H, broad), 2.45 (3H, singlet), and 7.32 and 7.78 (4H, AB-quartett) ppm, respectively.

The structure of **5a** was also assigned to di(p-toluamide) O,O'-carboxime from analytical and spectral data. Although the molecular ion peak of **5a** could not be detected, the mass spectrum of **5a** showed characteristic peaks at m/z 176 and 150 corresponding to the molecular ion peaks for **4a** and **1a**. The IR spectrum of **5a** showed characteristic absorption bands at 3480 and 3340 (NH_2), 1760 (C=O) and 1615 (C=N) cm^{-1}, respectively. In the ^{1}H-nmr spectrum, **5a** showed signals due to two amino and p-tolyl groups at 6.76 (4H, broad), 2.34 (6H, singlet) and 7.26 and 7.62 (8H, AB-quartett) ppm, respectively. The above assignment was also supported by the fact that **5a** could be converted to **4a** and **1a** by standing or heating in acetonitrile solution. The above structure was finally confirmed by a comparison of IR spectra and by a mixed melting point determination with an authentic sample derived from **1a** and phosgene following the method described in the literature.[3]

The structure of **4a** was assigned to 4,5-dihydro-3-(p-tolyl)-1,2,4-oxadiazol-5-one from analytical and spectral data and finally confirmed by a comparison of IR spectra and by a mixed melting point determination with an authentic sample derived from **1a** and ethyl chloroformate.[4] The structure of **6a** was determined by a comparison of IR spectra and by a mixed melting point determination with an authentic specimen.

Although the yields were not very good, the reaction is much interest from the standpoint of the reaction mechanism involved. The formation of 1,2,4-thiadiazole or 1,2,4-oxadiazole ring may be the result of deoxygenation or desulfurization process.

Benzamide oxime (**1b**), p-methoxybenzamide oxime (**1c**) and p-nitrobenzamide oxime

(**1d**) were reacted with **2** in a similar manner to the above affording the corresponding 3-aryl-4,5-dihydro-1,2,4-thiadiazol-5-one derivatives (**3**), 3-aryl-4,5-dihydro-1,2,4-oxadiazol-5-one derivatives (**4**) and di(benzamide) O,O'-carboxime derivatives (**5**), respectively. The mps and yields are listed in Table I.

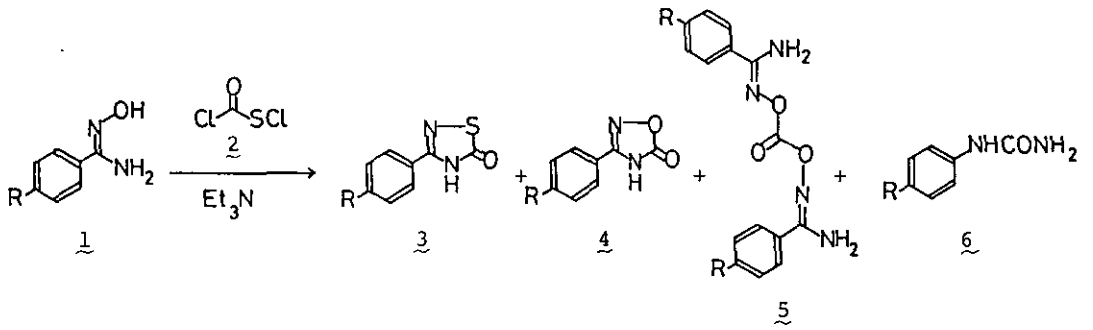


Chart 1

Table I. Reactions of Benzamide Oxime Derivatives (1) with CCSC (2)

Material 1	R	Temperature	Products [Mp (°C) and Yield (%)] 3 Mp	3 Yield	4 Mp	4 Yield	5 Mp	5 Yield	6 Mp	6 Yield
1a	CH_3	0°C	218	13	223[a]	16	145	3.0	184[b]	---
		reflux		17		21		trace[c]		3.0
1b	H	0°C	202	20	204[d]	11	128[e]	3.9	---	---
		reflux		13		5.0		trace		---
1c	OCH_3	0°C	226	22	214[f]	13	144	9.0	170	4.5
		reflux		11		24		trace		---
1d	NO_2	0°C	253	3.0	273[g]	3.0	---	---	---	---
		reflux		3.0		3.0		---		---

a) Lit. mp 229°C[Ref. 4] b) Lit. mp 182°C[Ref. 5a] c) Detected by TLC.
d) Lit. mp 208°C[Ref. 4] e) Lit. mp 129°C[Ref. 5b] f) Lit. mp 217°C[Ref. 4]
g) Lit. mp over 260°C[Ref. 5c]

In the case of p-methoxybenzamide oxime (**1c**), p-methoxyphenylurea (**6c**) was obtained in a 4.5% yield. When p-nitrobenzamide oxime (**1d**) was reacted with **2**, a large amount of a pale yellow amorphous substance was formed and products **3d** and **4d** were obtained in only 3% yield. p-Nitrobenzonitrile was also obtained in about 20% yield when the reaction was conducted either at 0°C or reflux.

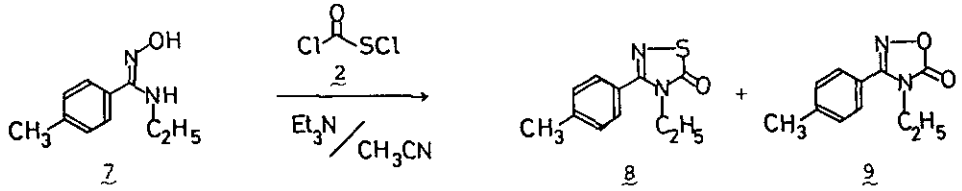
To improve the yields of 1,2,4-thiadiazol-5-one derivatives **3**, the reaction of **1a** with **2** was carried out under various conditions and the results are listed in Table II. Using sodium hydride as a catalyst at reflux, **3a** and **4a** were obtained in 22 and 26% yields, respectively. In this case, **5a** was not isolated in crystalline form and could be detected by TLC experiment. **6a** was also obtained in 3.0% yield.

Table II. Reactions of **1a** with **2** under Various Conditions.

No.	Solvent	Catalyst	Temperature	Yields of Products (%)			
				3a	**4a**	**5a**	**6a**
1	CH_3CN	Et_3N	0°C	13	16	3.0	----
2	CH_3CN	Et_3N	reflux	17	21	trace[a]	3.0
3	CH_3CN	DMA[b]	reflux	19	22	trace	3.0
4	CH_3CN	NaH	reflux	22	26	trace	3.0
5	CH_3CN	DMAP[c]	reflux	14	38	trace	trace
6	CH_3CN	DMAP	0°C	3.6	10	8.4	trace
7	CH_3CN	pyridine	reflux	6.3	3.8	6.0	3.0
8	THF	Et_3N	0°C	14	21	8.5	3.0

a) detected by TLC. b) N,N-dimethylaniline. c) 4-dimethylaminopyridine.

Treatment of N-ethyl-p-toluamide oxime (**7**) with **2** in the presence of triethylamine gave 4-ethyl-4,5-dihydro-3-(p-tolyl)-1,2,4-thiadiazol-5-one (**8**) and 4-ethyl-4,5-dihydro-3-(p-tolyl)-1,2,4-oxadiazol-5-one (**9**) as viscous oils in 29 and 13% yields, respectively. The structures of **8** and **9** were similarly assigned from analytical and spectral data described in the experimental section. The presence of the structural moiety Ar-C=N-S for compound **8** and Ar-C=N-O for compound **9** was confirmed from mass fragmentation peaks appearing at m/z 149 for **8** and m/z 133 for **9**, respectively.



7 8 9

Chart 2

A possible mechanism for the formation of products **3**, **4**, **5**, **6**, **8** and **9** is shown in Chart 3. It seems that the first step in the reaction of **1** with **2** maybe proceeds O- or N-carbonylation affording intermediates **A** and **C**. The resulting intermediate **A** may decompose with elimination of sulfur to give intermediate **B** which, on cyclization under dehydrochlorination, affords 3-aryl-4,5-dihydro-1,2,4-oxadiazol-5-one derivative **4**. When intermediate **B** reacts with **1**, di(benzamide) O,O'-carboxime derivative **5** is formed.

Intermediate **C** can cyclize under elimination of hydrogen chloride to form inter mediate **D** which, on reacting with CCSC, may undergo reductive ring-contruction to give 3-aryl-4,5-dihydro-1,2,4-thiadiazol-5-one derivative **3** through intermediates **E** and **F**.

The rearrangement of intermediate **A** may probably afford intermediate **G** which, on reacting with **1**, gives N-arylurea derivative **6** and intermediate **A**.[6]

The formation of products **8** and **9** can also be explained reasonably by mechanisms similar to the above.

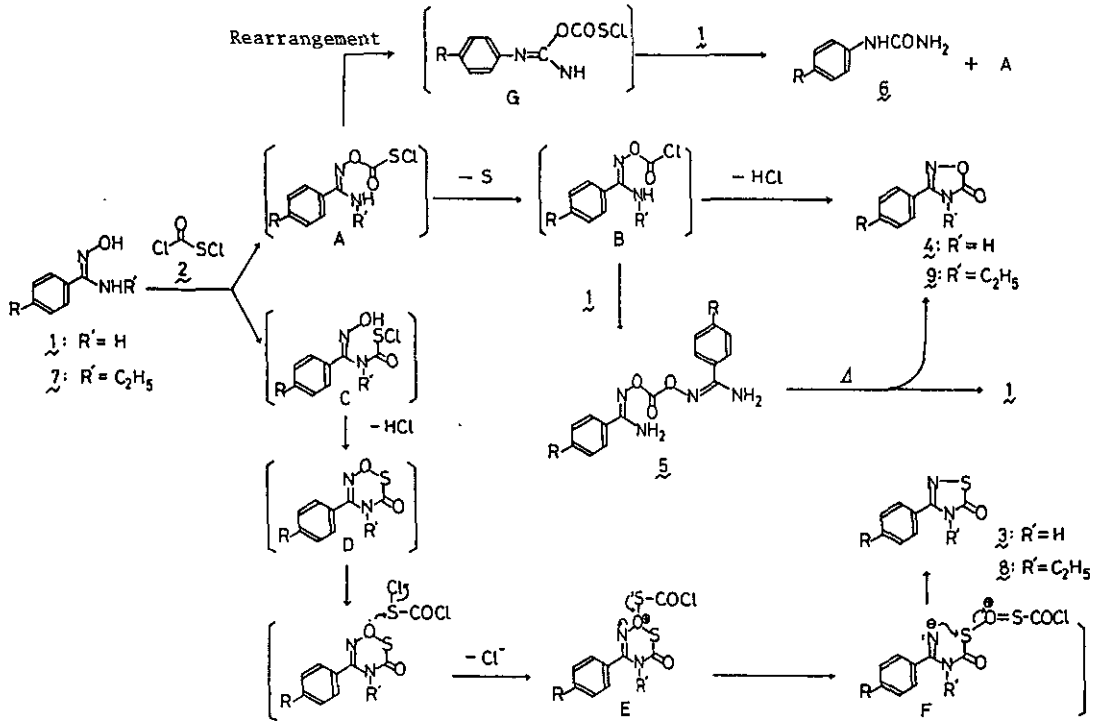


Chart 3

EXPERIMENTAL

All melting points were determined with a Yanagimoto hot-stage micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 215 spectrometer and the ^{1}H-nmr spectra, on Varian EM 390 and Bruker AM-400 spectrometers with TMS as an internal standard. The mass spectra were recorded on a JEOL JMS-D300 spectrometer.

Flash chromatography was carried out with a Kimura Kagaku flash chromatography apparatus and Kieselgel 60, using n-hexane:EtOAc mixture as the eluent under elution conditions described in the literature.[7] HPLC was performed with Kusano Kagaku KP-7H hplc apparatus and a CIG column (silica gel 50 μ) and UVILOG 254 detector.

MATERIALS.

The starting materials **1a-d** were prepared from the corresponding benzonitrile derivatives and hydroxylamine by the method described in the literature.[8]

Reaction of Benzamide Oxime Derivatives (1) with CCSC (2). General Procedure.

To a solution of **1** (0.5 mM) and triethylamine (50 mg, 0.5 mM) in 2 ml of dry acetonitrile, was added dropwise over a 15 minute period at 0°C a solution of **2** (66 mg, 0.5 mM) in 0.5 ml of dry acetonitrile. After stirring for 30 minutes at 0°C or reflux for 2 h, the reaction mixture was concentrated under reduced pressure to dryness. The residual solid was dissolved in 30 ml of EtOAc and washed with water (5 ml x 2). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to dryness. The residue was dissolved in a small amount of $CHCl_3$ and subjected to flash chromatography. Elution with n-hexane:EtOAc (2:1) and (3:2) gave four fractions. Each of these was subjected to HPLC using the same eluent to afford 3-aryl-4,5-dihydro-1,2,4-thiadiazol-5-one derivative **3**, 3-aryl-4,5-dihydro-1,2,4-oxadiazol-5-one derivative **4**, di(benzamide) O,O'-carboxime derivative **5**, and N-arylurea derivative **6** in this order. The physical and spectral data for these products are listed in Table III.

Reaction of p-Toluamide Oxime (1a) with CCSC (2) Using Various Basic Catalysts.

To a solution of **1a** (75 mg, 0.5 mM) and a base (0.5 mM) in 2 ml of dry solvent, was added dropwise over 15 minutes at 0°C a solution of **2** (66 mg, 0.5 mM) in

Table III. Physical and Spectral Data for Compounds **3**, **4** and **5**

Compd.[a]	Mp (°C)[b]	MS m/z (M^+)[c]	IR ν cm^{-1} [KBr]	^{1}H-nmr δ ppm [$CDCl_3$]
3a	218[A]	192	3150, 1660 1640	2.45 (3H, s, tolyl-CH_3), 7.32 and 7.78 (4H, AB_q, J=8 Hz, ArH), 11.1 (1H, b, NH)
3b	202[A]	178	3150, 1655	7.50-7.91 (5H, m, ArH), 11.4 (1H, b, NH)
3c	226[A]	208	3160, 1660 1650	3.88 (3H, s, OCH_3), 7.01 and 7.82 (4H, AB_q, J=9Hz, ArH), 10.9 (1H, b, NH)
3d	253[B]	223	3120, 1660 1640	8.19 and 8.37 (4H, AB_q, J=9 Hz, ArH), 13.7 (1H, b, NH)
4a	223[C]	176	3120, 1765	2.42 (3H, s, tolyl-CH_3), 7.31 and 7.78 (4H, AB_q, J=9 Hz, ArH), 11.4 (1H, b, NH)
4b	204[D]	162	3140, 1770	7.53-7.81 (5H, m, ArH), 11.2 (1H, b, NH)
4c	214[D]	192	3140, 1760	3.89 (3H, s, OCH_3), 7.03 and 7.68 (4H, AB_q, J=9 Hz, ArH), 10.0 (1H, b, NH)
4d	273[E]	207	3130, 1800	8.06 and 8.41 (4H, AB_q, J=9 Hz, ArH), 13.2 (1H, b, NH)
5a	145[B]	150*	3480, 3340 1760	2.34 (6H, s, tolyl-CH_3 x 2), 6.76 (4H, b, NH_2 x 2), 7.26 and 7.62 (8H, AB_q, J=9 Hz, ArH x 2)[DMSO-d_6]
5b	128[B]	136*	3500, 3455 1765	6.85 (4H, b, NH2 x 2), 7.46-7.75 (10H, m, ArH x 2)[DMSO-d_6]
5c	144[B]	166*	3500, 3450 1760	3.79 (6H, s, OCH_3 x 2), 6.72 (4H, b, NH_2 x 2), 7.00 and 7.67 (8H, AB_q, J=9 Hz, ArH x 2)[DMSO-d_6]

a) Analyses data [Found] are as follows:

3a ($C_9H_8N_2OS$): C, 56.25; H, 4.20; N, 14.58; S, 16.65 [C, 56.33; H, 4.14; N, 14.52; S, 16.45].

3b ($C_8H_6N_2OS$): C, 53.93; H, 3.40; N, 15.73; S, 17.96 [C, 54.22; H, 3.40; N, 15.93; S, 17.77].

3c ($C_9H_8N_2O_2S$): C, 51.92; H, 3.87; N, 13.46; S, 15.37 [C, 51.71; H, 3.79; N, 13.43; S, 15.51].

3d High-resolution MS m/z Calcd. for $C_8H_5N_3O_3S$ 223.0050; Found 223.0023.

5a ($C_{17}H_{18}N_4O_3$): C, 62.56; H, 5.56; N, 17.17 [C, 62.38; H, 5.58; N, 17.09].

5c ($C_{17}H_{18}N_4O_5$): C, 56.98; H, 5.06; N, 15.64 [C, 56.99; H, 5.06; N, 15.53].

b) Recrystallization solvent: [A] $CHCl_3$, [B] Acetone:EtOAc, [C] $CHCl_3$:EtOH, [D] $CHCl_3$:Acetone, [E] EtOAc:EtOH.

c) * Base peak. In the case of **5a-c**, the molecular ion peak was not detected.

0.5 ml of the same solvent as above. After stirring for 30 minutes at 0°C or refluxing for 2 h, the reaction mixture was concentrated under reduced pressure to dryness. The residue was treated with EtOAc followed by chromatographic workup in the similar manner to that described above. The yields, solvent and temperature used are listed in Table II.

Preparation of N-Ethyl-p-toluamide Oxime (7).

Following the method described in the literature,[9] a solution of p-tolualdehyde oxime (0.27 g, 2 mM) in 1 ml of DMF was reacted with N-chlorosuccinimide (0.53 g, 4 mM) over a 10 minute period at 35°C. After stirring the mixture for 1 h at that temperature, the spot of the starting material disappeared on TLC; 10 g of ice water were then added to the mixture which was subsequently extracted with Et_2O (10 ml x 3). The organic layer was combined and washed with water (10 ml x 3) and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to flash chromatography on a silica gel with n-hexane:EtOAc (15:1) as the eluent to give p-toluhydroxamoyl chloride (0.21 g, 62%), mp 53-55°C. This was used for amination without further purification.

To a solution of the above chloride (0.21 g, 1.23 mM) in 1 ml of Et_2O, was added dropwise a solution of triethylamine (0.21 g, 1.23 mM) and ethylamine (135 mg, 3 mM) in 2 ml of Et_2O over a 10 minute period at 0°C and the mixture was stirred for 1 h at that temperature. After removing a precipitate of triethylammonium chloride which had formed, the filterated solution was concentrated under reduced pressure to dryness. The residue was subjected to flash chromatography on a silica gel with n-hexane:EtOAc (4:3) as the eluent to give 0.16 g (76%) of colorless crystals of N-ethyl-p-toluamide oxime **7**, mp 73°C (from n-hexane:EtOAc mixture); IR (KBr) νcm^{-1}: 3400 (NH), 3230 (OH), 1640 (C=N); ^{1}H-nmr ($CDCl_3$) δ: 1.04 (3H, t, $\underline{J}$ = 8 Hz, $NCH_2C\underline{H}_3$), 2.34 (3H, s, tolyl-CH_3), 3.02 (2H, q, $\underline{J}$ = 8 Hz, $NC\underline{H}_2CH_3$), 7.12 and 7.30 (4H, AB_q, $\underline{J}$ = 7 Hz, ArH); *MS m/z*: 178 (M^+), 118 (base peak).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72.

Found: C, 67.30; H,7.87; N, 15.72.

Reaction of N-Ethyl-p-toluamide Oxime (7) with CCSC (2)

To a solution of **7** (90 mg, 0.5 mM) in 2 ml of dry acetonitrile, was added a

solution of **2** (66 mg, 0.5 mM) in 1 ml of the same solvent as above over a 15 minute period at 0°C. The reaction mixture was stirred for 30 minutes at that temperature and then concentrated under reduced pressure to dryness. The residue was dissolved in 30 ml of EtOAc, washed with water (10 ml x 2) and dried over sodium sulfate. After evaporation of the solvent, the residue was subjected to flash chromatography on a silica gel using n-hexane:EtOAc (5:1) as the eluent to give 4-ethyl-4,5-dihydro-3-(p-tolyl)-1,2,4-thiadiazol-5-one (**8**) and 4-ethyl-4,5-dihydro-3-(p-tolyl)-1,2,4-oxadiazol-5-one (**9**) as colorless viscous oils. After purification by HPLC using the same eluent as above, the yields of **8** and **9** were 29% (32 mg) and 13% (13 mg), respectively.

Compound **8** had the following physical and spectral properties: colorless viscous oil; IR ($CHCl_3$) ν cm^{-1}: 1675 (C=O); ^{1}H-nmr ($CDCl_3$) δ: 1.21 (3H, t, $\underline{J}$ = 8 Hz, $NCH_2C\underline{H}_3$), 2.43 (3H, s, tolyl-CH_3), 3.83 (2H, q, $\underline{J}$ = 8 Hz, $NC\underline{H}_2CH_3$), 7.31 and 7.41 (4H, AB_q, $\underline{J}$ = 8 Hz, ArH); MS m/z: 220 (M^+), 149 (base peak).

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.72; S, 14.53.

Found: C, 59.86; H, 5.49; N, 12.72; S, 14.70.

Compound **9** had the following physical and spectral properties: colorless viscous oil; IR ($CHCl_3$) ν cm^{-1}: 1770 (C=O); ^{1}H-nmr ($CDCl_3$) δ: 1.25 (3H, t, $\underline{J}$ = 8 Hz, $NCH_2C\underline{H}_3$), 2.45 (3H, s, tolyl-CH_3), 3.72 (2H, q, $\underline{J}$ = 8 Hz, $NC\underline{H}_2CH_3$), 7.36 and 7.46 (4H, AB_q, $\underline{J}$ = 8 Hz, ArH); MS m/z: 204 (M^+), 133 (base peak).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72.

Found: C, 64.79; H, 5.93; N, 13.70.

ACKNOWLEDGEMENTS

The authors are indebted to Mr. Shigeru Suzuki for conducting the elemental analyses, to Mr. Yasuo Shida for mass spectral measurement.

REFERENCES AND NOTES

1. A part of this work was presented at the 106th Annual Meeting of The Pharmaceutical Society of Japan, April 2, 1986.
2. G. Zumach and E. Kühle, Angew. Chem. internat. Edit., 1970, **9**, 54.
3. F. Tiemann and P. Krüger, Chem. Ber., 1885, **18**, 727.
4. K. Tabei, E. Kawashima, T. Takada and T. Kato, Chem. Pharm. Bull., 1982, **30**, 336.

5. [a] J. L. Boivin and A. Boivin, Can. J. Chem., 1951, **29**, 437.

[b] F. Tiemann and E. Falck, Chem. Ber., 1886, **19**, 1475.

[c] R. Buyle, Helv. Chim. Acta, 1963, **46**, 1073.

6. C. A. Cope, "Organic Reactions" Vol. 11, John Wiley & Sons, Inc., New York, 1960 p 45, and references cited therein.

7. W. C. Still, K. Kahn and A. Mitra, J. Org. Chem., 1978, **43**, 2923.

8. R. Lenaers, F. Eloy and C. Moussebois, Helv. Chim. Acta, 1962, **45**, 441.

9. [a] K. C. Liu, B. R. Shelton and R. K. Howe, J. Org. Chem., 1980, **45**, 3916.

[b] O. Exner, V. Jehlicka, A. Dondoni and A. C. Boicelli, J. Chem. Soc., Perkin Trans. II, **1974**, 567.

Received, 17th September, 1986