

## 1,2,4-Triazine IV ; 1,2,4-Triazine N<sub>4</sub>-Oxide 유도체와 POCl<sub>3</sub>와의 반응을 이용한 Chloro 및 Chloromethyl-1,2,4-Triazine 유도체 합성

李在璠\* · 權赫七 · 金憲坤

경북대학교 자연과학대학 화학과

(1992. 6. 1 접수)

## 1,2,4-Triazine IV ; Conversion of 1,2,4-Triazine N<sub>4</sub>-Oxides to Chloro- and Chloromethyl-1,2,4-Triazines with POCl<sub>3</sub>

Jae Keun Lee\*, Hyeok Chil Kwon, and Heon Gon Kim

Department of Chemistry, College of Natural Sciences, Kyungpook National University,  
 Taegu 702-701, Korea

(Received June 1, 1992)

It is well known that chloropyridines and chloroquinolines are easily formed from pyridine N-oxides and quinoline N-oxides respectively by the reaction of POCl<sub>3</sub><sup>1-3</sup>. Also 2- and 4-chloromethylpyridines are formed from 2- and 4-methylpyridine N-oxides<sup>4,5</sup>. The mechanism generally accepted is as following (Scheme 1).

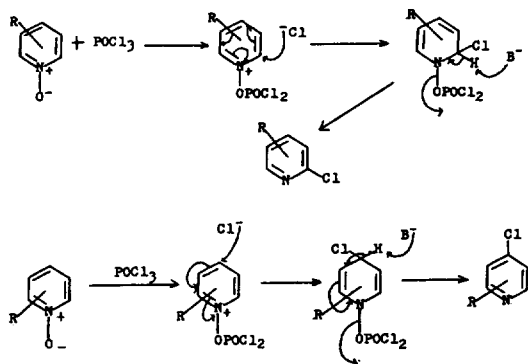
Even though there are not as many examples as pyridine N-oxides and quinoline N-oxides, the conversions of pyridazine N-oxides<sup>6,7</sup>, pyrazine N-oxides<sup>8,9</sup> and pyrimidine N-oxides<sup>10,11</sup> to chloropyridazines, chloropyrazines and chloropyrimidines respectively are well known. But there was no report about the reaction of 1,2,4-triazine N-oxides

with POCl<sub>3</sub> yet. We like to report our recent results of the conversion of 1,2,4-triazine N<sub>4</sub>-oxide to chloro and chloromethyl-1,2,4-triazines.

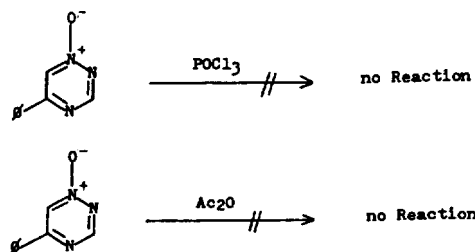
We have tried to synthesize 6-chloro-1,2,4-triazines from 1,2,4-triazine N<sub>1</sub>-oxides with POCl<sub>3</sub>. We could not have the expected products, but only unidentifiable tar was obtained. We also tried the conversion of 5-phenyl-1,2,4-triazine N<sub>1</sub>-oxide to 6-oxo-5-phenyl-1,6-dihydro-1,2,4-triazine with acetic anhydride, with only recovering the starting material back<sup>12</sup> (Scheme 2).

These results were rationalized with the fact that the larger electronegativity of nitrogen would reduce the nucleophilicity of oxygen because of the bigger contribution of resonance structure II and III (Scheme 3).

These results and rationalization prompted us



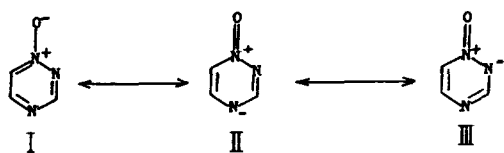
Scheme 1.



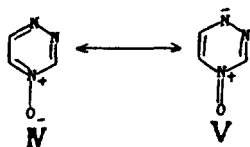
Scheme 2.

Table 1. pmr and mass spectra of chloro-1,2,4-triazine and chloromethyl-1,2,4-triazine

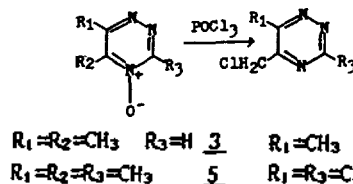
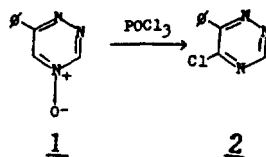
Compound	mp. (°C)	Yield (%)	PMR (CDCl <sub>3</sub> )	Mass : m/e (rel. intensity)
R <sub>1</sub> =φ R <sub>2</sub> =H R <sub>3</sub> =Cl	118~120	31	7.6(m, Ar) 8.1(m, Ar) 8.92(s, <sup>3</sup> H)	102(100) 191(11) 193(4)
R <sub>1</sub> =CH <sub>3</sub> R <sub>2</sub> =CH <sub>2</sub> Cl R <sub>3</sub> =H	oil	43	2.7(s, <sup>3</sup> CH <sub>3</sub> ) 4.65(s, <sup>5</sup> CH <sub>2</sub> ) 9.55(s, <sup>3</sup> H)	53(100) 129(43) 131(14)
R <sub>1</sub> =R <sub>3</sub> =CH <sub>3</sub> R <sub>2</sub> =CH <sub>2</sub> Cl	60~65	50	2.84(s, <sup>3</sup> CH <sub>3</sub> ) 2.9(s, <sup>6</sup> CH <sub>3</sub> ) 4.62(s, <sup>5</sup> CH <sub>2</sub> )	42(100) 157(25) 159(8)



Scheme 3.



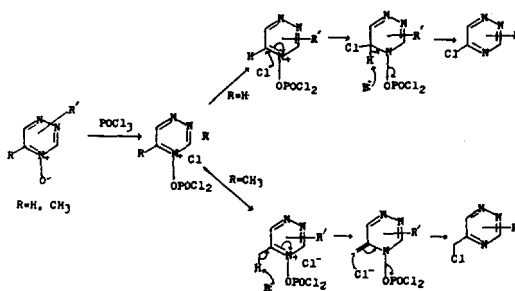
Scheme 4.



Scheme 5.

to try the conversion of 1,2,4-triazine N<sub>4</sub>-oxides, which are not possible to form a similar type of the resonance structure III, and therefore less reduction of nucleophilicity (Scheme 4), to chloro-1,2,4-triazines with POCl<sub>3</sub>.

6-Phenyl-1,2,4-triazine N<sub>4</sub>-oxide (1) was synthesized by the reported method<sup>13</sup> and treated with POCl<sub>3</sub>. The expected 5-chloro-6-phenyl-1,2,4-triazine (2) was obtained and identified by its pmr and mass spectra. The mass spectrum showed the molecular ion (M<sup>+</sup> = 191) and the chlorine isotope ratio of 191/193 was obtained to be 3/1. In its pmr, 3-H peak was appeared at δ 8.92 (singlet), phenyl peaks at δ 7.8 (multiplet) but 5-H at λ 9.3 was disappeared. 5,6-dimethyl-1,2,4-triazine N<sub>4</sub>-oxide<sup>13</sup> (3) was reacted with POCl<sub>3</sub> to produce the 5-chloromethyl-6-methyl-1,2,4-triazine (4) which was expected. Identification was done by its pmr and mass spectra. Chlorine isotope ratio of M<sup>-</sup> to M<sup>+</sup>+2 was shown to be right. Treatment of 3,5,6-trimethyl-1,2,4-triazine N<sub>4</sub>-oxide (5) with POCl<sub>3</sub> produced 5-chloromethyl-3,6-dimethyl-1,2,4-



Scheme 6.

triazine (6), which was tentatively assigned, since the 5-methyl protons are the most labile ones<sup>15</sup>. (Scheme 5).

Even though we never tried any experiment to clarify the reaction mechanism, we like to believe in the following general mechanism (Scheme 6).

Typical experimental procedure is as following. To the chloroform solution of phosphoryl chloride (5 ml, 55 mmol) the solution of 6-phenyl-1,2,4-triazine N<sub>4</sub>-oxide (200 mg, 1.1 mmol) in chloroform (5

ml) was added dropwise and the whole reaction mixture was refluxed for 5.5 hours. After cooling, the reaction mixture was poured into ice water. The reaction mixture was basified with 10% NaOH solution, and extracted by adding more chloroform. The chloroform solution was evaporated under reduced pressure yielding dark brown oil. The dark brown residue was chromatographed on silica gel with ethylacetate, as eluting solvent, yielding yellow crystal of 5-chloro-6-phenyl-1,2,4-triazine (80 mg, 31%).

#### REFERENCES

1. E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).
2. B. Riegel, G. R. Lappin, C. P. Albisetti, B. H. Dodson, L. G. Ginger, and R. H. Baker, *J. Am. Chem. Soc.*, **68**, 1229 (1946).
3. M. Hamana and H. Noda, *Chem. Pharm. Bull.*, **15**, 1380 (1967).
4. E. Ochiai, M. Fusimoto, and S. Ichimura, *Pharm. Bull. (Tokyo)*, **2**, 137 (1954).
5. T. Gato, *J. Pharm. Soc. Japan*, **75**, 1239 (1955).
6. S. Sato, *J. Pharm. Soc. Japan*, **82**, 1208 (1962).
7. S. Sato, *Chem. Pharm. Bull. (Tokyo)*, **11**, 337 (1963).
8. B. Klein, N. E. Hetmann, and M. E. O'Donell, *J. Org. Chem.*, **28**, 1682 (1963).
9. O. Akihiro, M. Sawako, I. Sachiko, T. Akiko, W. Hiroko, T. Mayumi, A. Yasuo, W. Tocuhiro, and K. Teruo, *J. Heterocycl. Chem.*, **19**, 465 (1982).
10. S. Takao, K. Sohichi, H. Yoshiaki, and Y. Hiroshi, *Heterocycles*, **20**, 991 (1983).
11. A. Y. Tikonov, L. B. Yolodarskii, O. A. Vakonova, and M. I. Podgornata, *Khim. Geterotsiki. Soedin.*, **1**, 110 (1981), through *C. A.* **95**, 7201m (1981).
12. J. K. Lee, M. D. Park, D. Y. Lee, and W. S. Kim, *J. Kor. Chem. Soc.*, **32**, 286 (1988).
13. H. Neunhoeffler, F. Weischedel, and V. Böhnisch, *Liebigs. Ann. Chem.*, **12**, 750 (1971).
14. V. Böhnisch, G. Bruzer, and H. Neunhoeffler, *Liebigs Ann. Chem.*, **18**, 1713 (1977).
15. W. W. Paudler and J. K. Lee, *J. Org. Chem.*, **36**, 3921 (1971).