N-N BOND CLEAVAGE OF 1-CHLOROPHTHALAZINE BY THE REACTION WITH YNAMINES

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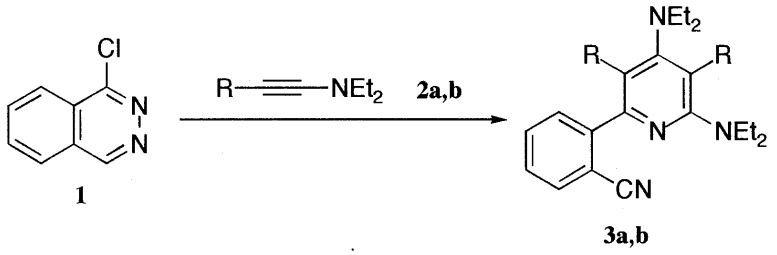
1-Chlorophthalazine reacts with two molar of ynamines to give penta-substituted pyridine derivatives by N-N bond cleavage of phthalazine ring. We realize this is common to other halo-substituted condensed pyridazines.

KEYWORDS phthalazine; bond cleavage; ynamine; condensed pyridazine

During the course of our investigations on a series of reactivities of condensed pyridazines with dienophiles, we found that the phthalazines having electron-withdrawing substituents undergo inverse Diels-Alder reaction with electron-rich dienophiles, such as enamines or ynamines. For example, 1-cyanophthalazine reacts with ynamines to give naphthalene derivatives by means of [4+2] cycloaddition followed by elimination of nitrogen.[1)]

In our search for the limitations of this reaction, an unusual reaction occured between 1-chlorophthalazine (**1**) and 2 eq. of ynamines (**2a,b**) to give penta-substituted pyridines (**3a,b**) with the N-N bond cleavage (Chart 1). To the best of our knowledge, no example of N-N bond in the phthalazine ring cleaved in the research of its reactivity.



Ynamines		Yield	
$R=CH_3$	**2a**	68%	**3a**
$R=CH_3CH_2$	**2b**	35%	**3b**

Chart 1

This reaction was finished within 10 min. at 80°C in a proper solvent, such as dioxane, or under absence of solvent.[2)] Using 1 eq. of ynamine, however, this reaction produced poor yields.

The proposed mechanism is as follows (Chart 2).

After the ynamine attacks 4- position of 1-chlorophthalazine, the very reactive ketene-immonium ion (**4**) is neutralized not by the delocalized anion in pyridazine ring moiety (intramolecular neutralization), but by another molecule of **2a** (intermolecular neutralization), and then it forms a six-membered ring (**6**). We realize the delocalization of anion in pyridazine ring moiety is influenced by the substituent in the pyridazine ring part, and therefore the ability of nucleophilicity is swayed. Thus the neutralization pathway of ketene-immonium ion is determined whether intra- or intermolecular. This type of reaction was observed in the synthesis of stabilized cyclobutadienes,[3)] and is evidence of our proposed mechanism.

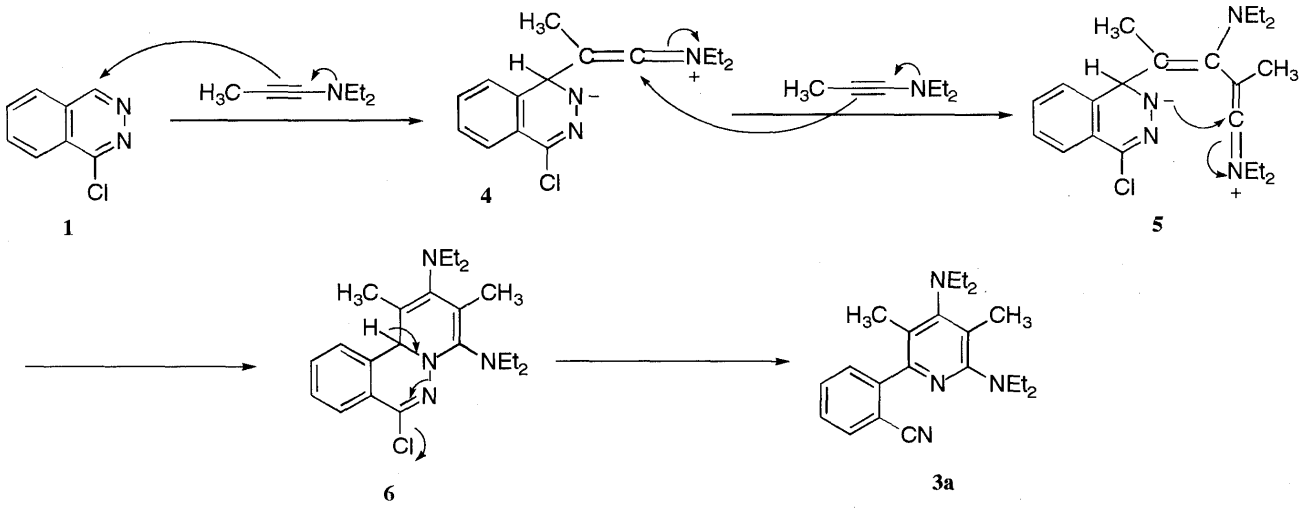


Chart 2

All spectral data[4] support the structure of **3a**, which was further determined by X-ray crystallography to be picrate of **3a** (Fig. 1).

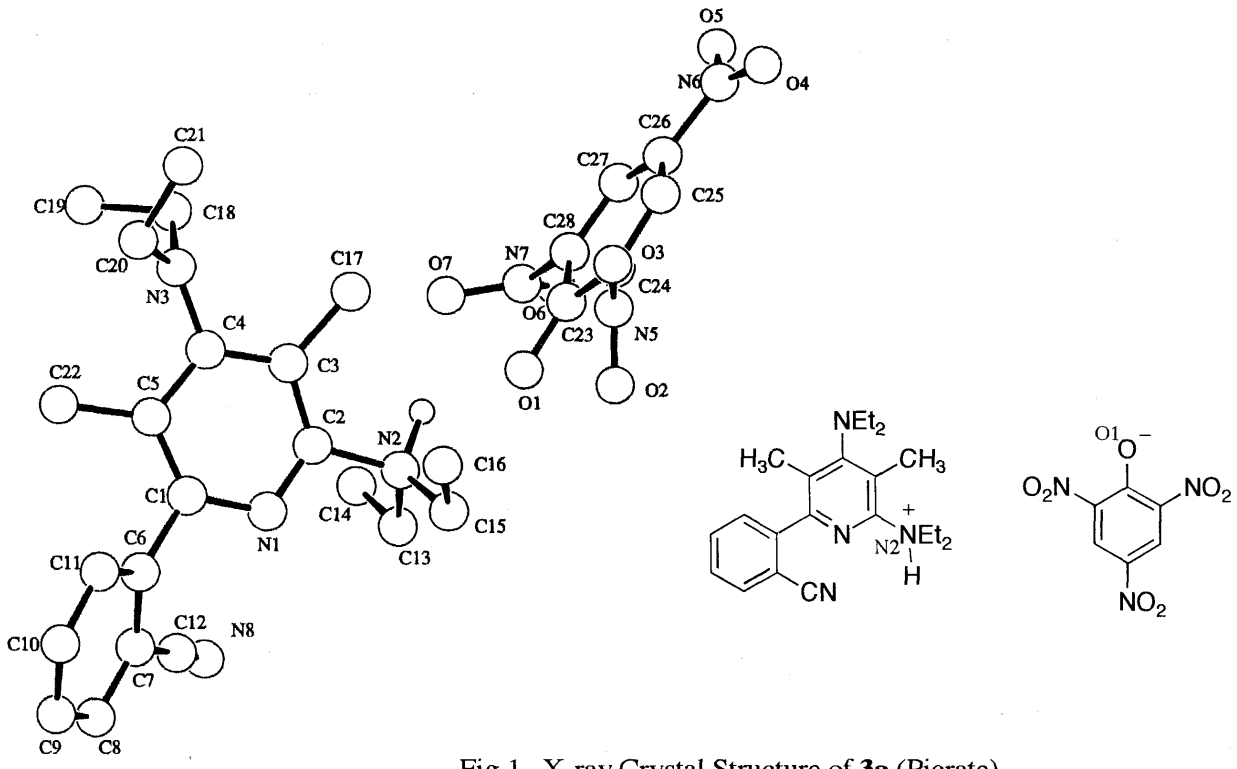
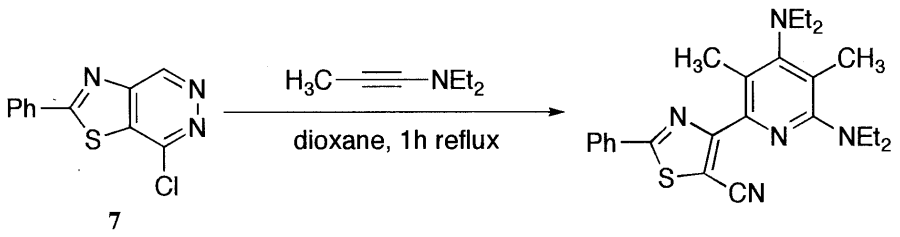


Fig. 1. X-ray Crystal Structure of **3a** (Picrate)

1-Substituted phthalazines having an electron-donating substituent (*e.g.*, OCH_3, SCH_3) did not react with ynamines. But this N-N bond cleavage reaction is observed in other halo-substituted condensed pyridazines such as **7**. It is considered that this new reaction can apply to other various halogen-substituted condensed pyridazines.



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In summary, halo-substituted condensed pyridazines underwent N-N bond cleavage with two molar of ynamines to give penta-substituted pyridine derivatives that have aryl or hetero aryl group at 2-position. This N-N bond cleavage reaction is a unique example, and the limitations and potential uses of this reaction are under investigation.

REFERENCES AND NOTES

1) E. Oishi, N. Taido, K. Iwamoto, A. Miyashita, T. Higashino, *Chem. Pharm. Bull.*, 38, 3268 (1990).

2) Preparation of **3a**: Compound **1** was dissolved in dioxane, and to this solution was added **2a** (2.1 molar eq.). The solution was heated to 80°C and stirred for 10min.. The reaction mixture was quenched with water and extracted with chloroform. The organic layer was washed with water and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was chromatographed (silica-gel, benzene/ chloroform = 10/1) to give **3a**.

3) R.Gompper, G.Seybold, *Angew. Chem.., Int. Ed. Engl*, 7, 824 (1968).

4) ^{1}H NMR($CDCl_3$): 7.72 (1H, ddd, J=7.7, 0.7, 0.7Hz), 7.60 (1H, ddd, J=7.7, 7.7, 1.3Hz), 7.52 (1H, ddd, J=7.7, 0.7, 0.7Hz), 7.42 (1H, ddd, J=7.7, 7.7, 1.3Hz), 3.19 (8H, q, J=7.1Hz), 2.20 (3H, s), 2.05 (3H, s), 1.07 (12H, t, J=7.1Hz); ^{13}C($CDCl_3$): 160.8, 158.2, 151.0, 146.1, 133.0, 132.0, 130.7, 127.4, 122.5, 121.9, 118.7, 112.8, 46.0, 44.7, 16.1, 15.9, 14.4, 13.1; IR(neat): 2230cm^{-1}; MS: m/e 350(M^+); Anal. Calcd. for $C_{28}H_{33}N_7O_7$(picrate): C, 58.02; H, 5.74; N, 16.92. Found: C, 57.78; H, 5.69; N, 16.72.

5) Empirical Formula: $C_{28}H_{33}N_7O_7$, Crystal System: triclinic, Space Group: $P\bar{1}$, Lattice Parameters: a=12.564(4)Å, b=13.658(2)Å, c=9.134(3)Å, α=107.36(2)Å, β=100.71(3)Å, γ=77.10(2)Å, V=1446.1(7)Å^3, D: 1.331g/cm^3, Z value: 2, R: 0.047. All measurements were made on a Rigaku AFC5R diffractometer with graphite, and the data were collected at a temperature of -100±1°C.

6) This paper is dedicated to Professor Yoshifumi Maki on the occasion of his retirement from Gifu Pharmaceutical University in March 1994.

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