

# Metal Mediated Dechlorination – A New Route to Nitriles

V.K. Tandon<sup>a</sup> and R.B. Chhor<sup>b\*</sup>

<sup>a</sup>Department of Chemistry, Lucknow University, Lucknow-226001, U. P., India

<sup>b</sup>Institut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31, D-93051 Regensburg, Germany

Received August 8, 2003; Accepted September 19, 2003

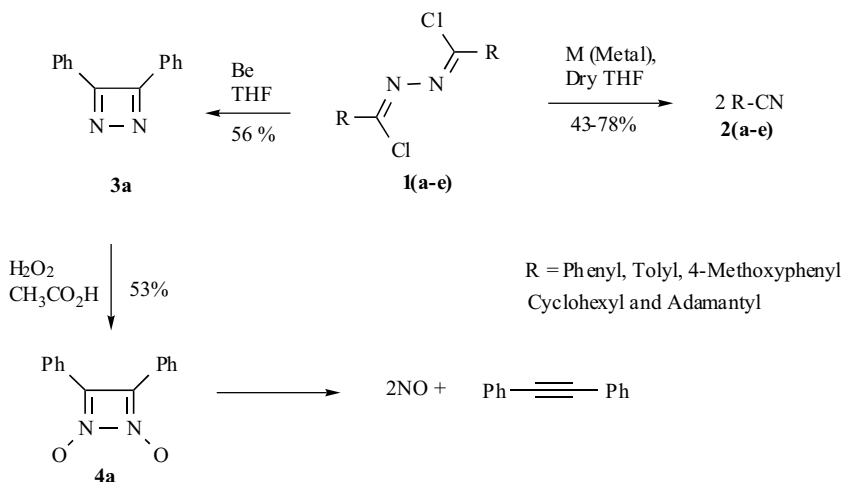
**Abstract:** 1,4-Dichloro-1,4-disubstituted-2,3-diaza-1,3-butadiene **1** undergo cyclodechlorination in presence of Be metal to form cyclazines **3a**. Reaction of **1** with Cu, Zn and Mn metals results in formation of nitriles **2**. Cyclazines **3** on further oxidation with H<sub>2</sub>O<sub>2</sub> in CH<sub>3</sub>COOH form NO donors, 1,2-dioxides **4**.

**Keywords:** Cyclodechlorination; chlorination; nitriles; cyclazines; NO donors.

Nitric oxide has been recognized as an important cellular mediator with widespread functions [1,2]. In addition NO donors have been found useful for treatment of respiratory, cardiovascular, infective and several other diseases [3].

Derivatives of 3,4-dihydro-1,2-diazete-1,2-dioxides have recently been investigated as NO donors *in vitro* and *in vivo* and found to be highly effective vasodilators [4]. Nitric oxide donors are known to liberate substituted alkenes and

The synthesis of presumably NO donor **4a** required cyclazine **3a**, while the syntheses of precursors, 1,4-dichloro-1,4-disubstituted-2,3-diaza-1,3-butadienes, **1 (a-e)** [10] for the nitriles **2 (a-e)** as well as cyclazine **3a** have been achieved by reaction of corresponding N',N'-diacylhydrazines<sup>11</sup> with PCl<sub>5</sub>. A few derivatives of **1** were isolated and characterized. The stereochemistry of **1a** was established by X-ray crystallographic studies [11] reveals that both aromatic rings



**Scheme 1.** Synthesis of **2(a-e)**, **3a** and **4a**.

nitric oxide as a by product, profoundly absorbed in blood vascular system [4,5].

In view of marked pharmaceutical utility of NO donors, we sought to develop methodology for the synthesis of hitherto unknown cyclazines **3** and convert these into 1,2-dioxides **4** for their pharmacological evaluation. Various unsuccessful attempts to prepare and characterize 1,2-diazacyclobutadiene (fully unsaturated diazetes) have been made earlier [6]. However, diazetidines [6], isosteres Diazetenes [7], 1,2-dihydro-1,2-diazetenes [8], and 3,4-dihydro-1,2-dihydro-1,2-diazetenes [9] are well known and characterized.

are twisted to each other due to intramolecular hydrogen bonding between chloro group and ortho hydrogen of the aromatic ring.

Treatment of **1** with different metals (Cu, Zn, Mn & Be) resulted in the formation of either nitriles **2 (a-e)** [12] or novel cyclazine (3,4-diphenyl-3,4-dihydro[1,2]diazete) **3a** from **1a** only [13].

Amongst four metals used for dechlorination of **1a**, Beryllium was found to be a metal of choice to yield cyclized product **3a** whereas other metals i.e. Cu, Zn, and Mn employed to **1 (a-e)** resulted in the generation of nitriles **2 (a-e)** (Scheme 1). On oxidation in the presence of H<sub>2</sub>O<sub>2</sub>/CH<sub>3</sub>COOH, compound **3a** was converted into 3,4-diphenyl-3,4-dihydro[1,2]diazete-1,2-dioxide **4a** [14] (Scheme 1), which is being investigated for its pharmacological properties as a NO donor.

\*Address correspondence to this author at the Institut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31, D-93051 Regensburg, Germany; E-mail: rb\_chhor@yahoo.co.in

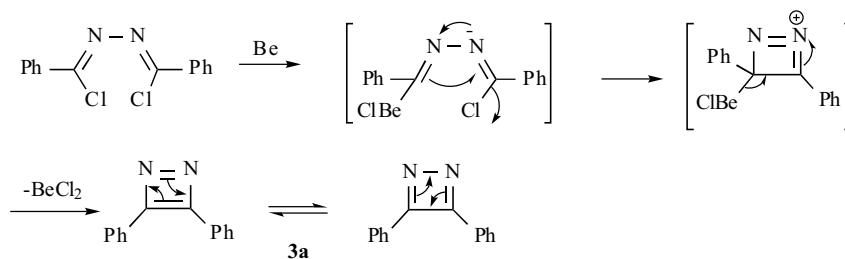


Fig. (1). Dechlorination mechanism towards **3a**.

Table 1.

Reactant	2	Yield (%)			m.p./b.p.
		Zn	Cu	Mn	
Phenyl	a	61	63	58	88°C / 20 torr(86°C/20) <sup>16</sup>
Tolyl	b	78	67	60	Pale YellowSyrup
4-Methoxyphenyl	c	72	60	53	57°C (60°C) <sup>17</sup>
Cyclohexyl	d	67	58	50	75°C/14 torr(57°C/12) <sup>18</sup>
Adamantyl	e	69	56	43	194°C (195.1°C) <sup>19</sup>

The plausible mechanism of cyclodechlorination of **1a** is presented in Fig. (1). Beryllium is less reactive than other alkali and alkaline earth metals as its atomic and ionic radii are comparatively too short and ionization energy too high. The outer orbital of transition metals occupy only 1 or 2 electrons, which are readily available to exhibit various type of reactions even in mild conditions e.g. metal chloride formation in presence of organic solvents and refluxing conditions as evidenced by Jochins *et al.* [15]. This facilitates the formation of cyclazine **3a** by elimination of BeCl<sub>2</sub>.

The probable mechanism of dechlorination towards formation of nitriles **2** is depicted in Fig. (2). The metal (Zn, Cu, Mn) bound with chlorine is more labile, which made feasible the extrusion of MCl<sub>2</sub> and formation of nitriles **2** (**a-e**) without driving force.

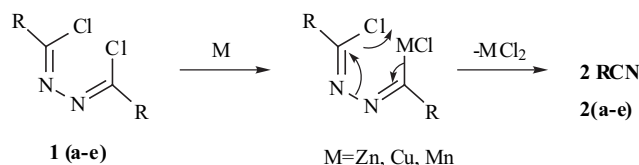


Fig. (2). Dechlorination mechanism towards **2**.

Nitriles **2** (**a-e**) were generated by reaction of **1** (**a-e**) with transition metals (Zn, Cu, Mn) under refluxing conditions using THF as a solvent [12]. Most of the synthesized nitriles are known and were characterized by means of IR spectroscopy and m.p. or b.p. (Table 1).

The cyanide stretching band in IR spectrum of the nitriles **2**(**a-e**) is observed at 2229, 2238, 2219, 2245 and 2270 cm<sup>-1</sup> respectively.

Cyclazine **3a** was prepared from **1a** in presence of Be metal and THF under refluxing [13]. The mass spectrum exhibited three signals M<sup>+</sup>+1, M<sup>+</sup> and M<sup>+</sup>-N<sub>2</sub> at 207, 206

and 177, respectively. Extrusion of N<sub>2</sub> from compound **3a** in the mass spectra reveals the existence of the cyclic product, which is in accordance with the assigned structure of **3a**.

Derivatization of compound **3a** is thought to be required in order to produce irrefutable evidence about its structure, since it can be considered as an analog of cyclobutadiene, which may be unstable and reactive because of anti-aromatic character. Although, sterically less hindered 1,2-dimethylcyclobutadiene has already been isolated on photolysis of dimethyl cyclobutenedicarboxylic anhydride [20]. Thus, N-oxide **4a** has been synthesized from **3a** in the presence of H<sub>2</sub>O<sub>2</sub> / CH<sub>3</sub>COOH by keeping two ideas in mind: at first to ascertain the structure and secondly N-oxides can be proved excellent NO-donors.

The N-oxide **4a** obtained from **3a** in presence of H<sub>2</sub>O<sub>2</sub>/CH<sub>3</sub>COOH [14] is being pharmacologically evaluated as NO donor. The synthesis of other NO donors of this series is in progress.

In summary we have demonstrated a simple and convenient synthesis of nitriles and devised an efficient synthetic route for cyclazine (3,4-disubstituted-3,4-dihydro-[1,2]-diazete) **3a** in moderate yields and elemental analysis grade purities by using commercially available beryllium metal powder in solution phase. The utility of NO donors derived from cyclazines is currently under investigation.

## ACKNOWLEDGEMENTS

The authors wish to thank to medicinal chemistry division, RSIC facilities of CDRI, Lucknow and Dr. H. Junjappa for his helpful discussion.

## REFERENCES

- [1] Bredt, D. S.; Snyder, S. H. *Annu. Rev. Biochem.*, **1994**, *63*, 175.

- [2] Schmit, H.; Walter, U. *Cell*, **1994**, 78, 919.
- [3] Lehmann, J. *Exp. Opin. Ther. Patents*, **2000**, 10, 559.
- [4] Utepbergenov, D. I.; Khramtsov, V. V.; Vlassenko, L. P.; Markel, A. L.; Mazhukin, D. G.; Tikhonov, A. Y.; Volodarsky, L. B. *Biochem. Biophys. Res. Commun.*, **1995**, 214, 1023.
- [5] Severina, I. A.; Ryaposova, I. K.; Volodarsky, L. B.; Mazhukin, D. G.; Tikhonov, A. Y.; Schwartz, G. Y.; Granic, V. G.; Grigor'ev, D. A.; Grigor'ev, N. B. *Biochem. Molec. Biol.*, **1993**, 30, 357.
- [6] Moore, J. A. *Chemistry of Heterocyclic compounds*; Weissberger A, Ed.; Interscience: New York, **1964**, 19 II, 916.
- [7] Nunn, E. E.; Warrenner, R. N. *J. Chem. Soc. Chem. Commun.*, **1972**, 818.
- [8] Effenberger, F.; Maier, R. *Angew. Chem. Int. Edit.*, **1966**, 5, 416.
- [9] Emeleus, H. J.; Hurst, G. L. *J. Chem. Soc.*, **1962**, 3276.
- [10] (a) Tandon, V. K.; Sharon, A.; Bandichhor, R.; Maulik, P. R. *Acta Crystallogr. E*, **2002**, E58, 869; (b) Kaszynski, P.; Young, V. G. Jr. *J. Am. Chem. Soc.*, **2000**, 122, 2087.
- [11] (a) Brown, B. J.; Elemens, I. R.; Neemsom, J.K. *Synlett.*, **2000**, 1, 131; (b) Tandon, V. K.; Chhor, R. B. *Synth. Commun.*, **2001**, 31, 1727.
- [12] Procedure for **2 (a-e)** : In separate experiments the transition metal 0.35 mol of activated Zn, Cu and Mn was added to a solution of 1,4-dichloro-1,4-disubstituted-2,3-diaza-1,3-butadiene **1 (a-e)** 1.39 g (0.005 mol) in dry THF (35 ml) and refluxed for 3h, solution concentrated *in vacuo*, column chromatography [SiO<sub>2</sub>-Hexane : EtOAc (10:1)]/ distillation at lower pressure gave the product **2 (a-e)** in 43-78% (Table 1).
- [13] Procedure for **3a** : 315 mg (35 mmol) of Be was added to a solution of 139 mg (0.5 mmol) **1a** in dry THF (5 ml), refluxed for 3 h, solution filtered through sintered crucible and concentrated *in vacuo* to give 57 mg of amorphous product **3a** which was stored at 0°C. R<sub>f</sub>(SiO<sub>2</sub>, PE:EE 1:1)=0.68; - m.p. = 97°C; - Yield = 56%; - <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>); δ = 7.33-7.53 (m, 6H, Ar-H), 7.97-8.08 (m, 4H, Ar-H); IR (film), ν=1444, 1483, 1568, 1691, 3058 cm<sup>-1</sup>; M<sup>+</sup> (m/z) 207 (11.7), 206 (95.5), 172 (13.2); Calculated: C, 81.53; H, 4.89; N, 13.58, Found: C, 81.68; H, 4.83; N, 13.49.
- [14] Procedure for **4a** : To a stirred solution of 3,4-diphenyl-3,4-dihydro-[1,2]-diazete **3a** (0.25 mmol; 51 mg) in 5 ml acetic acid, 1 ml 30% of H<sub>2</sub>O<sub>2</sub> was added and mixture was heated upto 90°C with stirring for 2 hr. Acetic acid was removed under vacuo and product chromatographed over (SiO<sub>2</sub>, PE:EE, 1:1) which gave 31.2 mg of **4a** as fluppy solid.; R<sub>f</sub>(SiO<sub>2</sub>, CHCl<sub>3</sub> : MeOH 1:1) = 0.80; - M.P. = 113°C; - Yield - 53%; - <sup>1</sup>H NMR (200 MHz, DMSO-d<sub>6</sub>); δ = 7.63 (m, 10H, Ar-H) IR (film), ν=1449, 1487, 1557 cm<sup>-1</sup>; M<sup>+</sup> (m/z) 238, 207, 146, 130, 104, 76; Calculated: C, 70.58; H, 4.23; N, 11.76, Found: C, 70.50; H, 4.28; N, 11.78.
- [15] Karich, G.; Jochims, J. C. *Chem. Ber.*, **1997**, 110, 2680.
- [16] Dauzonne, D.; Demmerseman, P.; Royer, R. *Synthesis*, **1981**, 739.
- [17] Muller, E.; Huber, H. *Chem. Ber.*, **1963**, 96, 670.
- [18] Chakraborti, A. K.; Kaur, G. *Tetrahedron*, **1999**, 55, 13265.
- [19] Wieringa, J. H.; Wynberg, H.; Strating, J. *Tetrahedron Lett.*, **1972**, 61, 2071.
- [20] Maier, G.; Mende, U. *Angew. Chem. Int. Edit.*, **1969**, 8, 132.