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ONE-POT CONVERSION OF *N*-ARYLGLYCINES TO SYDNONES EFFICIENTLY PROMOTED BY BIS-CHLORINE-1,4-DIAZABICYCLO[2.2.2]OCTANE COMPLEX Cl_2-DABCO IN THE PRESENCE OF $NaNO_2$/Ac_2O UNDER NEUTRAL CONDITION

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Abstract- Bis-chlorine-1,4-diazabicyclo[2.2.2]octane complex, (Cl_2-DABCO), has been found as an active chlorine complex for effective one-pot conversion of various *N*-arylglycines to sydnones in high yields (85-95%) under mild and neutral condition.

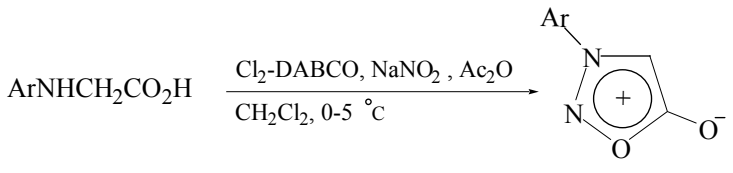
Sydnones **2**, which contain a five-membered heterocycle with a sextet of electrons, belong to a class of dipolar compounds known as 'mesoionic' and can be represented as hybrids of a number of mesoionic/ionic forms.[1-3] Sydnones undergo various transformations such as electrophilic substitution reactions that normally occur at the 4-position (if unsubstituted).[2,4] Due to their dipolar nature sydnones are eligible for 1,3-dipolar cycloadditions,[5] including reaction with unsymmetrical acetylenic dipolarophiles to produce a mixture of regioisomeric pyrazolines in high yield with carbon dioxide evolution and aromatization (a [4+2] cycloaddition similar to a Diels-Alder reaction).[6,7] Sydnones are also of biological and medicinal value as antibacterial,[8,9] antimalarial,[10] antitumour,[11] antihypertensive,[12] and anti-flammatory agents.[13]

Sydnones, as intrinsically neutral substances, were first reported by Earl and Mackney in 1935,[14] and are normally prepared by dehydrative cyclization of *N*-nitrosamino acids.[15] *N*-Nitrosamino acids were normally prepared by *N*-nitrosation of aminoacids upon treatment with nitrous acid generated from the reaction of sodium nitrite with an aqueous mineral acid.[16]

Previously, we have directed further work towards broadening the scope of our ongoing research on the applications of halogenated reagents in the synthesis of sydnones,[17] intending to avoid the limitations and

drawbacks ascribed to the previously reported methods such as strong acidic media used in nitrosation of *N*-arylglycines[18] prior to their cyclization to sydnones.[16] Earlier we reported our previous results on the application of *N,N,N',N'*-tetrabromobenzene-1,3-disolfonamide (TBBDS) for the effective conversion of *N*-arylglycines to the sydnones.[19]

In continuation of this effort, we have successfully examined the application of bis-chlorine-1,4-diazabicyclo[2.2.2]octane complex, (Cl_2-DABCO), as a more robust and efficient reagent for one-pot conversion of *N*-arylglycines to the corresponding sydnones under neutral conditions as depicted in Scheme **1**. The advantages allocated to the present protocol over our previously reported results on TBBDS are: (i) DABCO-Cl_2 complex is a novel air- and moisture-stable reagent which can be conveniently prepared from easily accessible and cheap 1,4-diazabicyclo[2.2.2]octane (DABCO) by a single-step procedure,[20] compared with TBBDS which has been prepared in three different steps; (ii) DABCO-Cl_2 complex is normally used in catalytic amount in reaction mixture (0.1 mmol per mmol of the substrate), whereas TBBDS is required in larger amounts to bring about the effective conversion of *N*-arylglycines to the sydnones; (iii) According to our suggested mechanism shown in Scheme **2**, DABCO-Cl_2 regent is automatically recovered (steps 5 and 7) in the reaction course; (iv) in all the reactions reported in this paper the *in situ* bromination of the synthesized sydnones was not detected, in contrast to the TBBDS which caused some subsequent bromination of the sydnones probably due to its excessive presence in the reaction mixture. The experimental results collected in table **1** indicate that DABCO-chlorine complex can effectively promote the conversion of the *N*-arylglycines (**1a-j**) to the sydnones (**2a-j**) in the presence of $NaNO_2$ and Ac_2O in CH_2Cl_2 in high yields (84-92%). It was shown that the most efficient conversions occur within 6-8 h at 0-5 ˚C when a catalytic amount of Cl_2-DABCO complex (0.1 mmol per mmol of *N*-arylglycines) is used in the reactions. No sydnones were afforded when these reactions were carried out in the absence of Cl_2-DABCO complex and *N*-arylglycines were recovered almost unreacted. In reliance on the well-established roles of acetic anhydride and also acetyl hypochlorite generated from the reaction of Ac_2O with hypochlorous acid during the reaction, in the cyclization of *N*-nitrosoglycines to sydnones,[15] we propose a possible mechanism for these reactions as shown in Scheme **2**, in which the cyclization of the intermediate *N*-nitrosoglycines is possibly activated by Cl_2-DABCO complex.

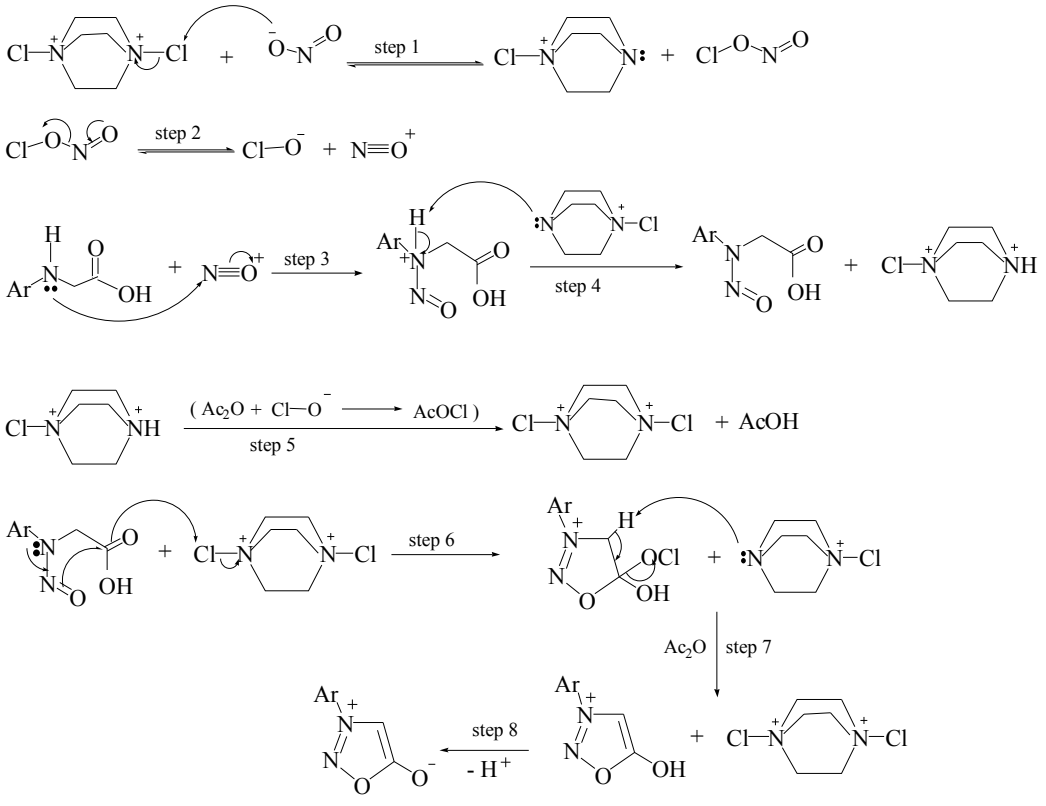


Scheme 1

Table 1 Conversion of the *N*-arylglycines (**1a-j**) to the sydnones (**2a-j**) with a combination of $NaNO_2$ /Ac_2O in CH_2Cl_2 catalyzed by Cl_2-DABCO complex.

Entry	Product[a]	Ar	Time (h)	Yield (%)[b]	Mp (°C)	
					Found	Reported[21, 22]
1	**2a**	*o*-$CH_3C_6H_4$	6.0	85	98	97
2	**2b**	*p*-$CH_3C_6H_4$	7.0	84	144	145
3	**2c**	*o*-$CH_3OC_6H_4$	6.5	87	97	97
4	**2d**	*p*-$CH_3OC_6H_4$	8.0	92	126	125
5	**2e**	*p*-$NO_2C_6H_4$	6.8	94	147	148
6	**2f**	*o*-$NO_2C_6H_4$	7.0	89	183	184
7	**2g**	*p*-ClC_6H_4	7.6	90	113	113
8	**2h**	*2,4*-$Cl_2C_6H_3$	7.8	91	95	96
9	**2i**	*p*-BrC_6H_4	7.5	90	138	137
10	**2j**	C_6H_5	7.7	88	134	135

[a]All the isolated products were characterized on the basis of their physical and ^1H NMR, ^{13}C NMR, IR spectral analysis and by direct comparison with literature data.[4, 14, 21, 22]
[b]Isolated yields.



Scheme 2

In conclusion, we have successfully examined the chlorine complex of DABCO as a novel, cheap and efficient, non-metallic air/water stable and easily recoverable catalyst for one-pot conversion of *N*-arylglycines to corresponding sydnones in high yields under neutral and mild condition.

EXPERIMENTAL

Chemicals were obtained from Merck and Fluka Chemical Companies. IR spectra were recorded using a

Shimadzu 435-U-04 spectrophotometer (KBr pellets) and ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ using 90 MHz JEOL FT NMR spectrometer. All melting points were determined on a Büchi 530 melting point apparatus, and reported uncorrected. DABCO-chlorine complex was prepared according to the literature as described below.[20]

Preparation of Cl_2-DABCO Complex:

To a magnetically stirred solution of 1,4-diazabicyclo[2.2.2]octane (DABCO) (6.72 g, 60 mmol) in chloroform (100 mL) was bubbled chlorine gas for 1 h at rt. The reaction mixture was then evaporated under reduced pressure to leave almost a pure solid product, yield = 98%. mp 125-130 ˚C (decomp). IR (KBr): 2800, 1500, 1380, 1000, 750 cm^{-1}. ^{1}H NMR (D_2O) δ: 3.2 (s, 12H, CH_2). ^{13}C NMR (22.5 MHz, D_2O) δ: 91.3.

Cl_2-DABCO-Promoted Conversion of the *N*-Arylglycines (1a-j) to the Sydnones (2a-j); General Procedure:

To a magnetically stirred solution of *N*-arylglycine **1** (2 mmol) in CH_2Cl_2 (50 mL), was added Cl_2-DABCO complex (0.04 g, 0.21 mmol), $NaNO_2$ (0.17 g, 2.5 mmol), and Ac_2O (0.31 g, 3 mmol) at 0-5 ˚C. After the complete conversion of the substrate in 6-8 h (Table **1**) as monitored by TLC using EtOAc/hexane mixture (1:1) as eluent, the reaction mixture was poured into water (5 mL), and then solid $NaHCO_3$ was added cautiously with stirring to remove the remaining glycines. The resulting mixture was filtered, the filtrate was extracted with CH_2Cl_2, and then the organic layer was separated, dried and evaporated in *vacuo* to leave the solid product **2**, which was further purified by recrystallization from EtOH. The products were characterized on the basis of their physical and spectral (IR, ^{1}H NMR, ^{13}C NMR) analysis and with direct comparison with the literature data.[4,14,21,22]

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