Catalytic Activity of 1,3-Dibromo-5,5-dimethylhydantoin (DBH) in the One-Pot Transformation of *N*-Arylglycines to *N*-Arylsydnones in the Presence of $NaNO_2/Ac_2O$ under Neutral Conditions: Subsequent Bromination of these Sydnones to their 4-Bromo Derivatives

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Abstract: 1,3-Dibromo-5,5-dimethylhydantoin (DBH) has been found to efficiently catalyze the one-pot conversion of various *N*-arylglycines through *N*-nitrosation and cyclization to sydnones in combination with $NaNO_2$ and Ac_2O in high yields (80–94%) under mild and neutral conditions. Also, it was shown that DBH can conveniently promote the bromination of these sydnones to their 4-bromo substituted congeners in excellent yields in DMF at room temperature.

Key words: nitrosation, *N*-arylglycines, sydnones, 1,3-dibromo-5,5-dimethylhydantoin (DBH), bromination

Sydnones such as **2** are unique archetypal members of that class of heterocyclic compounds known as mesoionic.[1] Sydnones were first prepared by Earl and Mackney in 1935,[2] and the greatest interest in them, ever since, stems from their biological activity as antibacterial,[3] antitumor,[4] antimalarial,[5] anti-inflammatory,[6] and antihypertensive[7] agents. Sydnones, also undergo a variety of transformations including electrophilic aromatic substitution at the 4-position (if unsubstituted),[8] 1,3-dipolar cycloaddition reactions to form pyrazoles or related species[9] and cleavage to hydrazines[2] or heterocycles[10] when treated with HCl. The ease with which these compounds undergo electrophilic aromatic substitutions is apparently similar to that of furan[1] and 3-arylsydnones **2** generally react with electrophiles to yield the corresponding 4-substituted derivatives. In the case of 3-arylsydnones, substitutions with a vast majority of electrophiles occur exclusively at the sydnone ring and not at the 3-aryl ring. This is probably attributable to deactivation of the aryl substituent by the electron-withdrawing effect of the sydnone ring N-3 position that bears a substantial fractional positive charge.[11,12]

Sydnones are intrinsically neutral substances that are normally prepared by dehydrative cyclization of *N*-nitrosamino acids.[13] *N*-Nitrosamino acids used in the synthesis of sydnones are themselves prepared from *N*-nitrosation of amino acids. *N*-Nitrosation is a well-known reaction in organic synthesis[14] that is usually accomplished with nitrous acid, generated by treatment of sodium nitrite with an aqueous mineral acid.[15]

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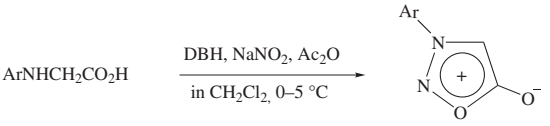
In connection with our ongoing studies on 1,3-dibromo-5,5-dimethylhydantoin (DBH) as a versatile and convenient reagent used in various transformations,[16–19] and also in order to avoid the drawbacks generally caused by the use of strong acidic media in nitrosation reactions, we wish, herein, to report on the use of DBH as a more robust and efficient catalyst for the one-pot conversion of *N*-arylglycines to sydnones under neutral conditions. In this work, we have observed that 1,3-dibromo-5,5-dimethylhydantoin (DBH) can efficiently catalyze the conversion of *N*-arylglycines **1a–j** to sydnones **2a–j** using sodium nitrite and acetic anhydride in CH_2Cl_2 with satisfactory yields (80–94%) (Scheme 1, Table 1). In reliance on the previously reported action of acetic anhydride in the cyclization of *N*-nitrosoglycines to sydnones,[2] we propose a possible mechanism for these reactions in five steps as shown in Scheme 2, in which the cyclization (step 4) of the intermediate *N*-nitrosoglycines is, probably, activated by acetyl hypobromite generated from the reaction of acetic anhydride with hypobromous acid.



Scheme 1

Among the aromatic substitution reactions of the sydnones, bromination reaction has attracted special interests. A number of methods including Br_2/Ac_2O,[21] $Br_2/NaHCO_3$ (and Br_2/KBr),[22] Br_2/NaOAc[23], and NBS[24] have been developed for the preparation of the 4-bromosydnones **3** from their 4-unsubstituted precursors. Most of these methods suffer from certain disadvantages including the use of expensive reagents, severe reaction conditions, low yields of the products, and problematic removal and recovering of the catalysts employed. In this regard, we were prompted to examine the DBH as a more robust and efficient reagent in the continuation of our research for bromination of 3-arylsydnones **2a–j**. The results obtained indicate the successful bromination of 3-arylsydnones **2a–j** to their 4-bromo derivatives **3a–j** using DBH in DMF at room temperature in good to excellent yields under mild conditions (Scheme 3).

Table 1 Conversion of *N*-Arylglycines **1a–j** to Sydnones **2a–j**

Entry	Product[a]	Ar	Time (h)	Yield (%)[b]	Mp (°C)	
					Found	Reported[20,21]
1	**2a**	2-$CH_3C_6H_4$	12.0	87	98	97
2	**2b**	4-$CH_3C_6H_4$	11.0	85	144	145
3	**2c**	2-$CH_3OC_6H_4$	11.5	90	97	97
4	**2d**	4-$CH_3OC_6H_4$	10.5	92	126	125
5	**2e**	2-$NO_2C_6H_4$	16.0	80	147	148
6	**2f**	4-$NO_2C_6H_4$	14.0	82	183	184
7	**2g**	4-ClC_6H_4	11.5	87	113	113
8	**2h**	2,4-$Cl_2C_6H_3$	16.0	83	95	96
9	**2i**	4-BrC_6H_4	11.0	90	138	137
10	**2j**	C_6H_5	10.0	94	134	135

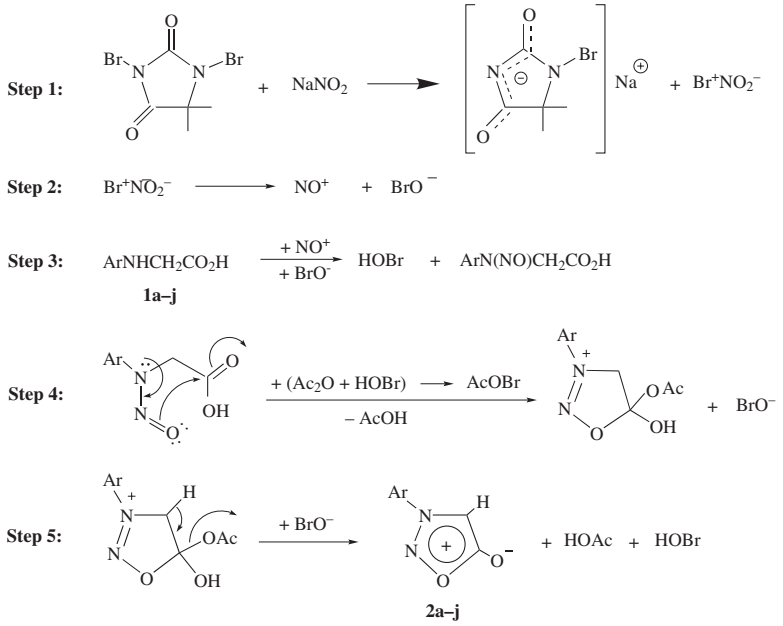
[a] All the isolated products were characterized on the basis of their physical properties and ^{1}H NMR, ^{13}C NMR and IR spectra and by direct comparison with literature data.[20,21]
[b] Isolated yields.

The transformations **2** → **3** were conducted using around two equivalents of the reagent DBH in DMF and, in all cases, the reactions completed in less than three hours at room temperature. The 4-bromo compounds **3a–j** were obtained in 94–99% yields (Table 2) after precipitation of the reagent, flash column chromatography (to remove polar impurities), and recrystallization from ethanol.

Chemicals were obtained from Merck and Fluka chemical companies. IR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained in $CDCl_3$ using a 90 MHz JEOL FT NMR spectrometer. All melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

Conversion of *N*-Arylglycines 1a–j to Sydnones 2a–j with $NaNO_2$/Ac_2O Catalyzed by DBH; General Procedure

To a magnetically stirred solution of *N*-arylglycine **1** (2 mmol) in CH_2Cl_2 (40 mL), was added 1,3-dibromo-5,5-dimethylhydantoin (DBH) (1.6 mmol), $NaNO_2$ (0.17 g, 2.5 mmol), and Ac_2O (0.31 g, 3 mmol) at 0–5 °C. After the completion of the reaction in 10–16 h (Table 1) as monitored by TLC, the mixture was poured into H_2O (5 mL), and then solid $NaHCO_3$ was added cautiously with stirring to

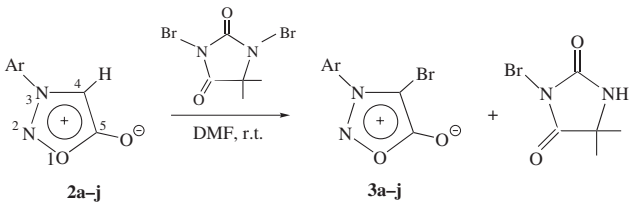


Scheme 2

Table 2 Bromination of 3-Arylsydnones **2a–j** to their 4-Bromo Derivatives **3a–j**

Entry	Substrate	Ar	Product[a]	Time (h)	Yield (%)[b]	Mp (°C)	
						Found	Reported[8,25,26]
1	**2a**	2-$CH_3C_6H_4$	**3a**	2.1	98	96	97
2	**2b**	4-$CH_3C_6H_4$	**3b**	2.0	99	88	89
3	**2c**	2-$CH_3OC_6H_4$	**3c**	2.3	97	110	110
4	**2d**	4-$CH_3OC_6H_4$	**3d**	2.2	99	106	107
5	**2e**	2-$NO_2C_6H_4$	**3e**	2.6	96	112	113
6	**2f**	4-$NO_2C_6H_4$	**3f**	2.5	90	154	154
7	**2g**	4-ClC_6H_4	**3g**	2.2	97	93	94
8	**2h**	2,4-$Cl_2C_6H_3$	**3h**	2.7	95	90	91
9	**2i**	4-BrC_6H_4	**3i**	2.1	96	98	97
10	**2j**	C_6H_5	**3j**	2.0	94	139	140

[a] All the isolated products were characterized on the basis of their physical properties and ^{1}H NMR, ^{13}C NMR and IR spectra and by direct comparison with literature data.[8,25,26]
[b] Isolated yields.



2a–j **3a–j**

Scheme 3

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 (Table 1). These products were characterized on the basis of their physical properties and also by their IR and ^{1}H NMR spectra with direct comparison with the literature data.[20,21]

Bromination of Sydnones 2a–j with DBH; General Procedure

To a stirred solution of 3-arylsydnone **2a–j** (1 mmol) in DMF (3 mL) was added DBH (0.548 g, 2 mmol), and the mixture was allowed to stir for 2.0–2.7 h at r.t. After complete conversion of the substrate as indicated by TLC, the mixture was poured into ice water, and extracted with CH_2Cl_2 (2 × 25 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to leave a brown residue, which was recrystallized from EtOH (95%) to yield pure tan crystals of **3a–j** in 94–99% yields (Table 2).

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