HETEROCYCLES, Vol. 68, No. 1, 2006, pp. 175 – 181. © The Japan Institute of Heterocyclic Chemistry
Received, 26th September, 2005, Accepted, 30th November, 2005, Published online, 2nd December, 2005. COM-05-10574

MICROWAVE-ASSISTED SYNTHESIS OF *N*-ARYLGLYCINES: IMPROVEMENT OF SYDNONE SYNTHESIS

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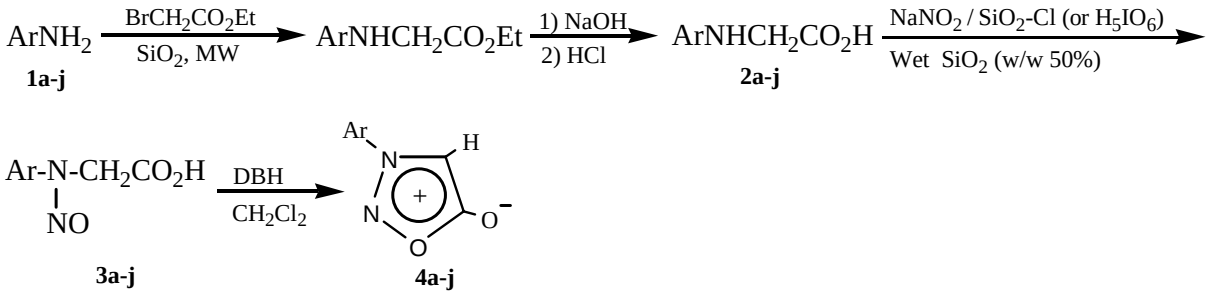
Abstract- Reactions of anilines with ethyl bromoacetate under microwave irradiation have afforded *N*-arylglycines that are subsequently converted to their *N*-nitroso derivatives with a combination of silica chloride or periodic acid, wet SiO_2 and sodium nitrite in CH_2Cl_2 with satisfactory yields. In the final step, the use of 1,3-dibromo-5,5-dimethylhydantoin (DBH) as a new and effective reagent for dehydration of *N*-nitroso-*N*-arylglycines to sydnones was successfully examined.

Sydnones such as **4** are dipolar heterocycles and archetypal members of the class of compounds known as mesoionic[1] which were first prepared by Earl and his co-workers in 1935.[2] Sydnones are of a biological importance: *inter alia* sydnones have been used efficaciously as antibacterial,[3] antitumour,[4] antimalarial,[5] anti-inflamatory,[6] and antihypertensive[7] agents. Their activity as MAO (monoamine oxidase) inhibitors has also been reported.[8] Sydnones can also undergo a variety of transformations including electrophilic aromatic substitution (at the 4-position, if unsubstituted),[1,9-14] cleavage with HCl to form hydrazines[2] or heterocycles,[15] hydrolysis with hot alkali to regenerate the *N*-nitrosamino acids[16] and 1,3-dipolar cycloadditions to form pyrazoles or related species.[17] Sydnones (**4)** constitute a well-investigated intrinsically neutral substances which are normally prepared by dehydration of *N*-nitrosamino acids.[18]

In a total preparative scheme to the sydnones (**4a-j)**, we wish herein to report some useful modifications in an easy synthesis of *N*-arylglycines (**2a-j)** from microwave-assisted reactions of the anilines (**1a-j)** with ethyl bromoacetate in the presence of SiO_2 and their subsequent conversion to the sydnones (**4a-j)**

through their intermediate formation of *N*-nitrosoglycines (**3a-j)** (Scheme **1**). As shown in Table **1**, the results obtained from the reactions of the anilines (**1a-j)** with ethyl bromoacetate indicate that the application of the microwave irradiation can considerably increase the efficiency of these reactions to produce the *N*-arylglycines (**2a-j)** in satisfactory yields (89-95%) and reduce the reaction times when compared with the classical thermal conditions.

Scheme 1



(**a**) Ar = C_6H_5; (**b**) Ar = 2-MeC_6H_4; (**c**) Ar = 4-MeC_6H_4; (**d**) Ar = 4-$MeOC_6H_4$; (**e**) Ar = 2-$NO_2C_6H_4$; (**f**) Ar = 4-$NO_2C_6H_4$; (**g**) Ar = 4-ClC_6H_4; (**h**) Ar = 2,4-$Cl_2C_6H_3$; (**i**) Ar = 4-BrC_6H_4; (**j**) Ar = 2-$MeOC_6H_4$

Table 1: Silica-supported conversion of the anilines (**1a-j)** to the *N*-arylglycines (**2a-j)** with ethyl bromoacetate under microwave irradiation condition.

Entry	Substrate	Product[a]	Reaction Time		Yield (%)[b]		mp (˚C)
			MW (min)	Thermal (h)	MW	Thermal	
1	**1a**	**2a**	7.0	21.0	93	65	83
2	**1b**	**2b**	8.0	16.0	85	52	121
3	**1c**	**2c**	5.0	15.0	90	66	132
4	**1d**	**2d**	4.0	14.0	89	49	135
5	**1e**	**2e**	5.3	15.5	87	48	140
6	**1f**	**2f**	5.0	15.0	90	53	165
7	**1g**	**2g**	4.8	14.0	91	56	102
8	**1h**	**2h**	7.2	24.0	83	51	98
9	**1i**	**2i**	6.3	18.0	88	57	105
10	**1j**	**2j**	4.3	15.0	85	47	118

[a]Products were characterized on the basis of their physical, IR and ^{1}H-NMR spectral analysis and by direct comparison with literature data, (**2a)**,[2] **(2b, 2h),**[18] (**2c, 2f, 2g**),[19] (**2d, 2e, 2j**),[20] (**2i)**.[21] [b]Purified Yields.

In the next stage of our preparative scheme to the sydnones (**4a-j)**, we have examined a mild and heterogeneous method to nitrosate the *N*-arylglycines (**2a-j)** to the *N*-nitrosoglycines (**3a-j)**. *N*-Nitrosation of glycines is a well-established reaction used in synthesis of sydnones.[22] Nitrous acid generated from treatment of sodium nitrite with strong mineral acids in water or aqueous alcohol is the most generally

employed reagent in nitrosation reactions.[23] In this work, we have examined the combination of $NaNO_2$ with silica chloride (**I**) or H_5IO_6 (**II**) in the presence of wet SiO_2 (w/w 50%) in CH_2Cl_2 as an efficient and simple reagent for nitrosation of the *N*-arylglycines (**2a-j)** prepared in the preceding stage (Scheme **1**) under mild and heterogeneous condition. The results obtained from these reactions are summarized in Tables **2** and **3**. It is to mention that this reagent has been previously reported for the nitrosation of secondary amines.[24,25]

Table 2: Nitrosation of the *N*-arylglycines (**2a-j)** (2 mmol) with a combination of silica chloride (**I**) and $NaNO_2$ in the presence of wet SiO_2 (w/w 50%) in CH_2Cl_2 at 0-5 ˚C.

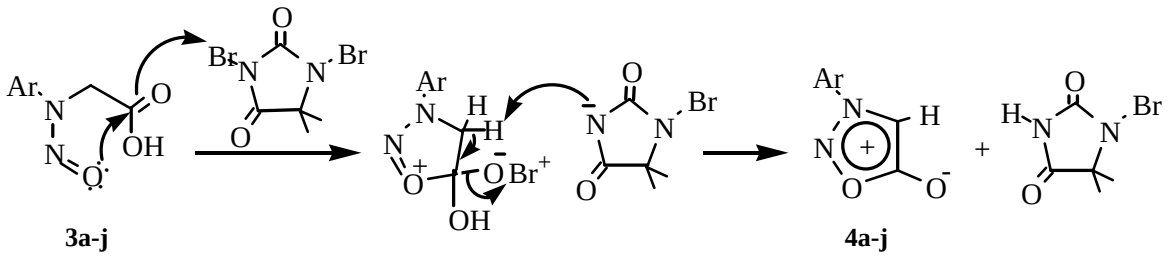
Entry	Substrate	Product[a]	Reagent (**I**) (gr)	Time (h)	Yield (%)[b]	mp (˚C)
1	**2a**	**3a**	0.6	2.5	90	72
2	**2b**	**3b**	0.5	2.0	92	111
3	**2c**	**3c**	0.4	2.2	93	120
4	**2d**	**3d**	0.5	1.7	92	121
5	**2e**	**3e**	0.5	2.1	91	132
6	**2f**	**3f**	0.6	2.0	93	148
7	**2g**	**3g**	0.6	2.3	95	91
8	**2h**	**3h**	0.7	2.0	88	89
9	**2i**	**3i**	0.6	2.4	90	96
10	**2j**	**3j**	0.5	1.8	89	110

[a]Products were characterized on the basis of their physical, IR and ^{1}H-NMR spectral analysis and by direct comparison with literature data, (**3a)**,[2] (**3b, 3h**),[18] (**3c, 3f, 3g**),[19] (**3d, 3e**, **3j**),[20] (**3i**).[21] [b]Purified Yields.

Dehydration of *N*-nitroso-*N*-arylglycines to their corresponding sydnones with trifluroacetic anhydride in CH_2Cl_2 has been previously reported.[2,20,26,27]

In connection with our ongoing studies on 1,3-dibromo-5,5-dimethylhydantoin (DBH) as an efficient and versatile reagent used in various transformations,[28-30] we successfully examined DBH as a more robust and less expensive reagent in the final step of scheme **1** to effectively convert the *N*-nitroso-*N* arylglycines (**a-j)** to the sydnones (**4a-j)** in CH_2Cl_2 under mild conditions in high yields (85-94%) (Table **4**). A possible mechanism proposed for these cyclization reactions by DBH is shown in Scheme **2**.

Scheme 2



3a-j **4a-j**

Table 3: Nitrisation of *N*-arylglycines (**2a-j)** (2 mmol) with a combination of H_5IO_6 (**II**) and $NaNO_2$ in the presence of wet SiO_2 (w/w 50%) in CH_2Cl_2 at 0-5 ˚C.

Entry	Substrate	Product[a]	Reagent (**II**) (gr)	Time (h)	Yield[b] (%)	mp (˚C)
1	**2a**	**3a**	1.8	2.3	88	72
2	**2b**	**3b**	1.6	1.9	92	111
3	**2c**	**3c**	1.8	2.0	90	120
4	**2d**	**3d**	1.7	1.9	94	121
5	**2e**	**3e**	1.6	2.2	89	132
6	**2f**	**3f**	1.7	2.0	91	148
7	**2g**	**3g**	1.5	2.3	94	91
8	**2h**	**3h**	1.6	2.1	90	89
9	**2i**	**3i**	1.7	2.2	90	96
10	**2j**	**3j**	1.8	1.7	89	110

[a]Products were characterized on the basis of their physical, IR and ^{1}H-NMR spectral analysis and by direct comparison with literature data, (**3a)**,[2] (**3b, 3h**),[18] (**3c, 3f, 3g**),[19] (**3d, 3e**, **3j**),[20] (**3i**).[21] [b]Purified Yields.

Table 4: Dehydrative cyclization of the *N*-nitroso-*N*-arylglycines (**3a-j**) to the corresponding sydnones (**4a-j**) by DBH in CH_2Cl_2 at 0-5 ˚C.

Entry	Product[a]	Yield (%)[b]	mp (˚C)	IR (KBr) (cm^{-1})	^{1}H-NMR ($CDCl_3$) (ppm)
1	**4a**	87	134	3110, 1760, 941, 735	6.38 (s, 1H, CH_{syd}), 7.40-6.60 (m, 5H, Ar)
2	**4b**	80	98	3100, 1770, 940, 730	2.40 (s, 3H, CH_3), 6.47 (s, 1H, CH_{syd}), 7.60-7.20 (m, 4H, Ar)
3	**4c**	78	144	3110, 1760, 940, 735	2.20 (s, 3H, CH_3), 6.31 (s, 1H, CH_{syd}), 7.70-7.20 (m, 4H, Ar)
4	**4d**	88	126	3100, 1770, 940, 730	4.20 (s, 3H, CH_3), 6.53 (s, 1H, CH_{syd}), 7.60-7.10 (m, 4H, Ar)
5	**4e**	82	147	3120, 1780, 950, 740	6.67 (s, 1H, CH_{syd}), 8.40-7.60 (m, 4H, Ar)
6	**4f**	86	184	3119, 1775, 944, 738	6.60 (s, 1H, CH_{syd}), 8.20-7.40 (m, 4H, Ar)
7	**4g**	81	113	3110, 1760, 940, 730	6.57 (s, 1H, CH_{syd}), 7.90-7.30 (m, 4H, Ar)
8	**4h**	86	95	3120, 1768, 945, 737	6.71 (s, 1H, CH_{syd}), 8.40-7.60 (m, 3H, Ar)
9	**4i**	88	138	3119, 1762, 943, 730	6.52 (s, 1H, CH_{syd}), 7.80-7.10 (m, 4H, Ar)
10	**4j**	89	97	3117, 1755, 940, 750	4.30 (s, 3H, CH_3), 6.50 (s, 1H, CH_{syd}), 7.90-7.30 (m, 6H, Ar)

[a]Products were characterized on the basis of their physical, IR and 1H-NMR spectral analysis and by direct comparison with literature data, (**4a**),[2] (**4b, 4h**),[18] (**4c, 4f, 4g**),[19] (**4d, 4e, 4j**),[20] (**4i**).[21] [b]Purified yields.

EXPERIMENTAL

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 reported uncorrected.

Step 1: Preparation of *N*-arylglycines (2)

To a stirred mixture of ethyl bromoacetate (1.70 mg, 10 mmol) and SiO_2 (5 g), was added the aniline (**1)** (10 mmol), and the resulting mixture was irradiated (300 Watt) for a few min (Table **1**) at rt. The resulting solid mixture was washed with water (3x10 mL), filtered, and then treated with 10% aqueous solution of sodium hydroxide (10 mL) in ethanol (2 mL) for 10 min under reflux until the complete dissolution occurred. The mixture was allowed to cool to rt, acidified with aqueous HCl (0.1 %), then extracted with CH_2Cl_2 (2x20 mL), and the extract was dried over anhydrous $MgSO_4$, evaporated in *vacuo* and finally recrystallized from ethanol to yield the pure corresponding *N*-arylglycines (**2)** (Table **1**).

Step 2: *N*-Nitrosation of the *N*-arylglycines (2) to the *N*-nitroso-*N*-arylglycines (3)

(i) To a mixture of the *N*-arylglycine (**2)** (2 mmol) and silica chloride (Table **2**) was added wet SiO_2 (w/w 50 %) (0.4 g) and $NaNO_2$ (0.2 g, 3 mmol) in CH_2Cl_2 (10 mL) and the resulting mixture was vigorously stirred at 0-5 ºC for a few h (Table **2**). After the completion of the reaction that was monitored by TLC, the resulting reaction mixture was extracted with dichloromethane (2x20 mL), dried over anhydrous $MgSO_4$, and then evaporated under reduced pressure to yield the *N*-nitrosoarylglycine (**3)** which was purified by recrystallization from ethanol (Table **2**). The structures of these compounds were established on the basis of their IR, ^{1}H-NMR and ^{13}C-NMR spectral analysis and direct comparison with the literature data.[2,18-21]

(ii) In a flask, a suspension of the *N*-arylglycine (**2)** (2 mmol), H_5IO_6 (Table **3**), wet SiO_2 (w/w 50 %) (0.4 g) and $NaNO_2$ (0.2 g, 3 mmol) in CH_2Cl_2 (10 mL) was stirred at 0-5 ºC for a few h (Table **3**). After the completion of the reaction that was monitored by TLC using EtOH/petroleum ether (1:8), the reaction mixture was filtered, then the filterate dried over anhydrous $MgSO_4$, and evaporated in *vacuo* to leave a solid residue which was recrystallized from ethanol to yield highly pure *N*-nitrosoarylglycine **(3)** (Table **3**).

Step 3: Cyclization of the *N*-nitroso-*N*-arylglycine (3) to the sydnones (4)

To a magnetically stirred solution of the *N*-nitrosoglycine **(3)** (5 mmol) in CH_2Cl_2 (5 mL), was added 1,3-dibromo-5,5-dimethylhydantoin (DBH) (1.45 mg, 5 mmol) at 0-5 ºC . After 4 h, the reaction mixture was poured into water (5 mL), and then solid sodium bicarbonate was added cautiously with stirring to remove the remaining glycines. The organic layer was separated, dried over anhydrous $MgSO_4$, and then

evaporated in *vacuo* to leave the solid product **(4)**, which was further purified by recrystallization from ethanol. These products were characterized on the basis of their IR and ^{1}H-NMR spectral data given in the Table **4** and with direct comparison with literature data.[2,18-21]

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