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Synthesis of 1,4-Diaryl-piperazine-2,5-diones: New Behavior of *N,N*-Dimethylformamide Dimethyl Acetal (DMFDMA)

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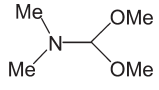
Abstract: Reactions of chloroacetamides (**5**) with *N,N*-dimethylformamide dimethyl acetal gave 1,4-diaryl-piperazine-2,5-diones **11a**–**e** in good yield, rather than 1,5-diaryl-3,7-dimethoxy-1H,5H-[1,5]diazocine-2,6-diones (**9a**–**e**).

Keywords: α-chloroacetamides 1,4-diarylpiperazine-2,5-diones, condensation, dimerization, *N,N*-dimethylformamide dimethyl acetal

Formamide acetals are useful reagents.[1,2] They have two sites of attack in their structure. The first one is nucleophilic—the nitrogen atom that carries two electron-repelling groups (methyl groups)—and the other is electrophilic—the carbon that carries two electron withdrawing groups (methoxy groups). We concentrate on *N,N*-dimethylformamide dimethyl acetals (DMFDMA) (**1**).



(**1**)

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Dedicated to Dr. Basil J. Wakefield on the occasion of his 73rd birthday.

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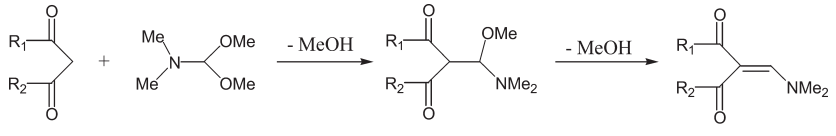
Their main application has been functional group transformations,[3] but they may also be regarded as one-carbon synthons in the construction of carbon skeletons. One type of reaction that is potentially valuable for the latter purpose involves 1,3-dicarbonyl compounds **1** to give enamines **4**.[2] We have reported that these enamines **4** were used as precursors in the synthesis of pentasubstituted pyridines[4–6] and pentasubstituted benzene[7] (Scheme 1).

In an extension of our studies, we now report reactions of *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (**1**) with chloroacetamides[8] **5**. This reaction was expected to afford the chloroenamine derivatives[4] **6**, which are important precursors that can be used for further heterocyclic syntheses. After the addition of DMFDMA, a highly water-soluble white precipitate was formed, but the ^{1}H NMR spectra of the product showed the disappearance of the -NMe_2 group and the appearance of a singlet at δ 4.5 ppm (Table 1). Also, the mass spectra of the product showed a molecular ion peak at higher values than compounds **5** and the absence of chlorine, so the product of these reactions is not **6** (Scheme 2). One possible pathway for further reaction of **6** is shown in Scheme 2, in which nucleophilic attack on **6** by the produced MeOH gives **7**. Protonation by the relased HCl affords the salt **8**, and subsequent dimerization with the elimination of dimethylamine hydrochloride leads to the formation of 1,5-diaryl-3,7-dimethoxy-1*H*,5*H*-[1,5]diazocine-2,6-diones **9**.[9]

However, the mass spectra of the products did not show the molecular ion corresponding to structure **9**, and their ^{1}H NMR spectra showed a singlet signal at about $\delta_H = 4.5$ ppm and aromatic protons only. The proton of the diazocine ring does not appear. Also, ^{13}C NMR showed the presence of a methylene group, not a methoxy group, which indicates that the products are not **9**. Scheme 3 shows a possible alternative pathway, in which *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (**1**) act as a nucleophile that attacks the carbon carrying the chlorine in chloroacetamides (**5a**–**e**) to afford the salt (**10a**–**e**),[10] dimerization with elimination of DMFDMA then gives 1,4-diarylpiperazine-2,5-diones **11**.

The identity of the main product **11** was established by MS, ^{1}H NMR, and elemental analysis as shown in Tables 1 and 2. We have found that Okawara et al.[11] reported the syntheses of various 1,4-disubstituted 2,5-diketopiperazines by intermolecular condensation of halocarboxamides using a reaction

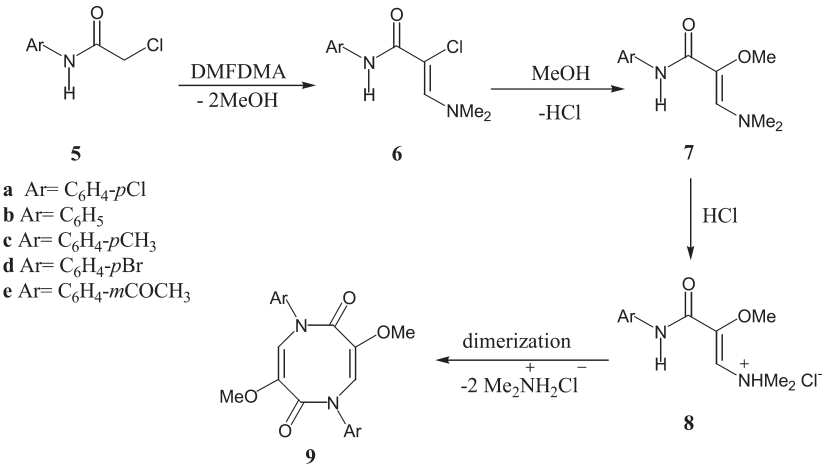


Scheme 1.

Table 1. Physical and spectroscopic data of 1,4-diaryl-piperazine-2,5-diones (**11a–e**)[a]

Product	Yield (%)	Mp (°C)	Molecular formula	Molecular weight	IR (KBr) $\nu(cm^{-1})$	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
5a	60	242	$C_{16}H_{12}Cl_2N_2O_2$	335.18	1656, 1590	4.43 (s, 4H), 7.22–7.24 (d, 4H, $J = 7.1$ Hz), 7.35–7.37 (d, 4H-Ar AB, $J = 7.2$ Hz) equal integrals
5b	58	275 (267[11])	$C_{16}H_{14}N_2O_2$	266.29	1656, 1612, 1582	4.53 (s, 4H), 7.3–7.46 (m,10H-Ar)
5c	54	262	$C_{18}H_{18}N_2O_2$	294.35	1656, 1590	2.64 (s, 6H), 4.59 (s, 6H), 7.49–7.63, 7.81–7.95 (m, 8H-Ar)
5d	62	144	$C_{16}H_{12}Br_2N_2O_2$	424.09	1692, 1656, 1582	4.42 (s, 4H), 7.15–7.18 (d, 4H, $J = 6.95$ Hz), 7.50–7.52 (d, 4H-Ar AB, $J = 6.93$ Hz) equal integrals
5e	42	168	$C_{20}H_{18}N_2O_4$	350.37	1653, 1580	2.63 (s, 6H), 4.49 (s, 4H), 7.27–7.95 (m, 8H-Ar).

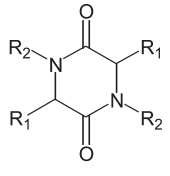
[a]Satisfactory microanalysis obtained: C, H, N $\pm$ 0.3.



Scheme 2.

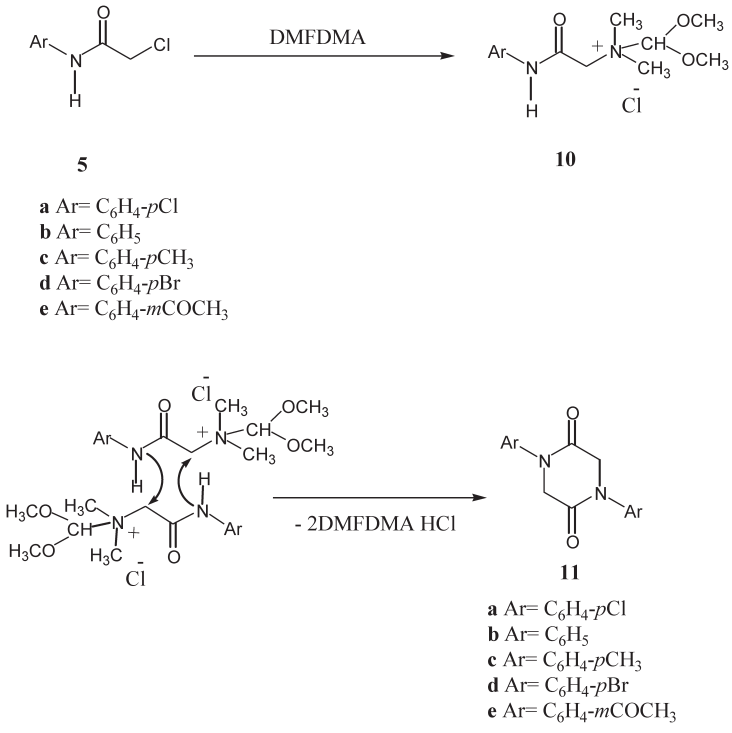
system comprising a mixture of dichloromethane and 50% aqueous sodium hydroxide solution in the presence of a solid phase-transfer catalyst. Among the compounds whose syntheses are reported in Okawara et al. are 1,4-dibenzylpiperazine-2,5-dione (**11f**), 1,4-diphenylpiperazine-2,5-dione (**11b**), and 1,4-diphenyl-3,6-dimethylpiperazine-2,5-dione (**11g**). The reference does not report any use for the products synthesized.

Cavicchioni et al.[12] reports the preparation of both *N,N′*-dialkylpiperazines and 2-amino-2-haloalkyloxazolidones by intermolecular condensations of the same reactants used in the syntheses described by Okawara et al. Cavicchioni et al. do not give much detail on the reaction system utilized, but apparently employed a polar organic solvent system rather than a two-phase system with a phase-transfer catalyst. Also, several 1,4-diaryl-2,5-piperazinediones were prepared from halogen-substituted acetamide derivatives.[13]



11

f, R_1= H, R_2= $C_6H_5CH_2$
g, R_1=CH_3, R_2= C_6H_5



a Ar= C_6H_4-*p*Cl
b Ar= C_6H_5
c Ar= C_6H_4-*p*CH_3
d Ar= C_6H_4-*p*Br
e Ar= C_6H_4-*m*$COCH_3$

Scheme 3.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 17100 FTIR spectrometer as KBr disks. NMR spectra were recorded on Bruker AC300 spectrometer at 400 MHz for solutions in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard unless otherwise recorded at the Department of Chemistry, Sultan Qaboos University, Al-Kha, Oman. Mass spectra were obtained on Finnigan 4500 (low-resolution) spectrometers using electron impact (EI) assay at the Micro-analytical Center, Cairo University, Giza, Egypt. Chloroacetamides (**5a**–**e**) were prepared according to literature procedure.[8] *N,N*-Dimethylformamide dimethyl acetal (DMFDMA) was purchased from Merck.

General Procedure for 1,4-Diaryl-piperazine-2,5-diones 11a–e

A mixture of α-chloroacetamides (**5a**–**e**) (10 mmol) and dimethylformamide dimethyl acetal (1.19 g, 10 mmol) in dry dioxane (20 mL) was refluxed for

Table 2. ^{13}C NMR and DEPT ^{13}C NMR data of 1,4-diaryl-piperazine-2,5-diones **11c–e**

Product	^{13}C NMR (DMSO) δ C	DEPT 135	DEPT 90	DEPT 45
5c	21.49 (CH_3), 53.93 (CH2), 125.54, 130.47, 137.47, 137.94 (CH-Ar), 164.45 (CO)	21.06 (CH_3), −53.49 (CH_2) 124.86, 130.04 (CH-Ar)	125.17, 129.77 (CH-Ar)	
5d	53.50, 9 (CH_2), 120.53, 126.81, 133, 138.78 (CH-Ar), 164.05 (CO)	−53.06 (CH_2), 126.38, 132.56 (CH-Ar).	126.43, 132.62 (CH-Ar)	53.50 (CH_2), 126.81, 133 (CH-Ar)
5e	27.07 (CH_3), 53.55 (CH_2), 12470, 127.79, 129.98, 130.12, 133.75, 140.47 (Ar), 164.35(CO), 197.31 (CO)	26.66 (CH_3), −53.15 (CH_2) 124.34, 127.40, 129.66, 129.70 (CH-Ar)	124.32, 127.45, 129.71, 129.75 (CH-Ar)	27.09 (CH_3), 53.58 (CH_2), 124.70, 127.8 129.99, 130.13 (CH-Ar)

6 h. The solution was filtered while hot. After cooling, the solid obtained was collected by filtration and purified by recrystallization from ethanol to afford the corresponding **11a–e**. Yields and other data are compiled in Tables 1 and 2.

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