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A Single-Step Synthesis of 1,3,4,6-Tetraaryl-5-aryliminopiperazin-2-one

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Abstract. Chemical diversity is a strong driver in drug discovery, and chemical reactions that produce multi-substituted heterocycles can result in significant chemical diversity. Here, we report a reaction that leads to highly substituted piperazinone derivatives in a single step. This was discovered accidently while reacting phenylglyoxal and anilines under Povarov conditions. We elucidated the structure of the compound formed when 2-(4-trifluoromethyphenyl)-2-oxoacetaldehyde was reacted with 4-methoxyaniline as (1,4-bis(4-hydroxyphenyl)-5-[(4-hydroxyphenyl)imino]-3,6-diphenylpiperazin-2-one) (**5e**). The structure was confirmed after extensive spectral analyses, including correlation spectroscopy, nuclear Overhauser effect spectroscopy, heteronuclear single quantum correlation spectroscopy, and heteronuclear multiple-bond correlation nuclear magnetic resonance spectroscopy, in addition to high-resolution mass spectrometry. This reaction is unprecedented and can potentially be exploited as a short route to highly diversified heterocycles.

Keywords: Piperazine; Lewis Acid; Glyoxal; Cyclization

Introduction

The reaction of arylglyoxals with arylamines has been reported to yield products other than simple mono- and di-imines. Table 1 lists the conditions and products of the reaction of phenylglyoxal with aniline and other substituted congeners reported in the literature. In the case of Entry 1, for instance, a modified Möhalu–Bischler indole synthesis method was used to form 2-phenylindole from phenylglyoxal and aniline[1]. Further, the oxidative amination of glyoxals can be efficiently used to prepare α-ketoamidines (Entry 2)[2] or α-ketoamides (Entry 3)[3]. Moreover, Povarov conditions have been used (Entry 4) in a three-component reaction involving an alkene (e.g., dihydrofuran), aniline, and phenylglyoxal in the presence of a Lewis acid catalyst to obtain 4-benzoyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline[4].

We were interested in designing modular peptidomimetics such as 1,2,3,4-tetrahydroquinolines with appended 2-acyl groups as new antiviral agents (Scheme 1)[5]. Therefore, we reacted phenylglyoxal (**1**), aniline (**2**), and olefins (**3**) under Povarov conditions[6] with the aim of obtaining 4-oxysubstituted compounds **4** (Scheme 1).

Results and Discussion

2.1. LC/MS analysis of the Povarov reaction involving phenylglyoxal, aniline, and alkenes

The outcome of the reaction shown in Scheme 1 was found to be affected more by the structure of the alkene component than by the type of catalyst used (Table 2). In this regard, vinyl ethers (Entries 1–6) gave the expected Povarov product (1,2,3,4-tetrahydroquinoline) in variable yields that depended on the catalyst used (Entries 1–6). Meanwhile, the Povarov tetrahydroquinoline product was not detected when vinyl acetate or vinyl pivalate was used as the dienophile (Entries 7–13). A plausible explanation for these results is that the acyl group of the vinyl ester has an electron-withdrawing effect that decreases the electron density on the alkene and limits its ability to initiate the 4+2 Povarov annulation[7]. However, we noticed a peak at *m/z* 494 $(M+1)^+$ during electrospray ionization (ESI) liquid chromatography–mass spectrometry (LC/MS) under all conditions and with all catalysts (2, 3, and 7–13). Accordingly, we conclude that the vinyl ester plays no role in the formation of the product.

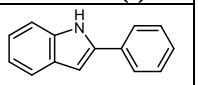
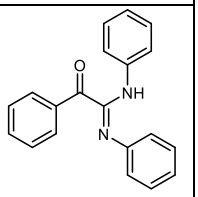
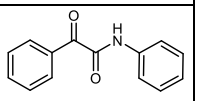
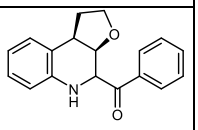
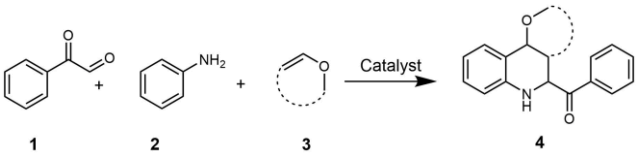
Entry	Conditions	Product(s)
1	[$PdBr_2$(rac-BINAP)], H_2	
2	[Cu], CH_3COONa, air	
3	[Cu], Pyridine (base), air	
4	Salen-AlCl, 2,3-dihydrofuran	

Table 1. Non-imine products produced from the reaction of phenylglyoxal and aniline

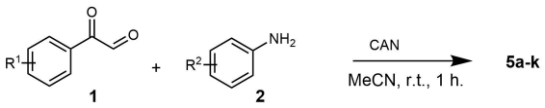
Entry	Alkene	Catalyst	Product[1]	Side Product (M+1)m/z
1	2,3-Dihydropyran	CAN[2]	26%	ND[3]
2	2,3-Dihydrofuran	CAN	35%	M+22% (m/z 494)
3	2,3-Dihydrofuran	Montmorillonite KSF[4]	6%	34% (m/z 494)
4	Ethyl vinyl ether	CAN	31%	ND[3]
5	Ethyl vinyl ether	Montmorillonite KSF	52%	ND
6	Ethyl vinyl ether	Montmorillonite K10[4]	46%	ND
7	Vinyl acetate	CAN	ND	50% (m/z, 494)
8	Vinyl acetate	Montmorillonite KSF	ND	16% (m/z 494)
9	Vinyl acetate	Montmorillonite K10, DCM	ND	59% (m/z 494)
10	Vinyl acetate	Montmorillonite K10, $MgSO_4$	ND	54% (m/z 494)
11	Vinyl acetate	Montmorillonite K10	ND	56% (m/z 494)
12	Vinyl acetate	$Yb(OTf)_3$	ND	ND
13	Vinyl pivalate	Montmorillonite K10	ND	37% (m/z 494)

Table 2. Reactions of aniline with phenylglyoxal and alkenes in presence of various catalysts

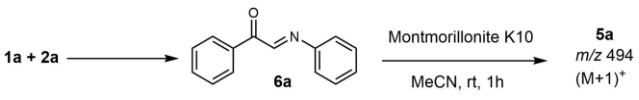


Scheme 1. The Povarov reaction of phenylglyoxal, aniline, and various alkenes in the presence of the catalysts listed in Table 1.

Therefore, we performed the same reaction without a vinyl ester and, as expected, obtained the same product with a molecular mass of 493 (Scheme 2). Moreover, we prepared imine **6** (Scheme 3) by reacting aniline with phenylglyoxal[8]. The Schiff base, **6**, was isolated and dissolved in acetonitrile and mixed with a Lewis acid (Montmorillonite K10) for 1 h. The LC/MS of the reaction indicated that product **5a** was formed in a yield of 27%.



Scheme 2. Povarov conditions for the reactions of arylglyoxals and arylamines without an alkene.



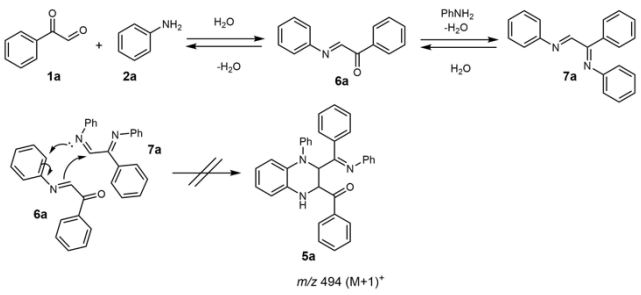
Scheme 3. Formation of **5a** from Schiff base **6a** under catalysis in the presence of a Lewis acid.

We next endeavored to determine the structure of unexpected product **5a** (Table 3, Entry 1); consequently, the reaction was performed using a substituted phenylglyoxal and aniline. The use of *p*-methoxyphenylglyoxal as the aldehyde component (Scheme 2) yielded **5b** with an *m/z* of 554 $(M+1)^+$ (Table 3, Entry 2). The difference in *m/z* values is due to the presence of the two methoxy groups and is attributable to *p*-methoxyphenylglyoxal. In a third experiment, product **5c** with *m/z* 584 $(M+1)^+$ was detected in the crude product when the reaction was performed using phenylglyoxal and *p*-anisidine (Table 3, Entry 3). The difference in *m/z* between **5c** and the unsubstituted aniline **5a** is due to three methoxy groups and is attributable to the involvement of three 4-methoxyaniline molecules in the reaction. Another simple calculation provided an additional clue as to what had occurred during the reaction. The sum of the masses of three aniline molecules and two phenylglyoxal molecules is 547 (i.e., 493 + $3H_2O$). The underlying logic here is that two phenylglyoxal molecules take part in a reaction with three aniline molecules, during which three water molecules are lost. Given that the final product **5a**, which had an *m/z* of 494 $(M+1)^+$, was formed without the loss of any other units or groups, we initially assumed that a Povarov-type cyclization reaction had occurred (Scheme 4), which was based on the fact that we were using Povarov reaction conditions. Therefore, we speculated that a quinoxaline derivative had formed through the cycloaddition of imine **6a** and diamine **7a** (Scheme 4).

Table 3. LC/MS and HRMS data for the reactions of arylglyoxals with arylamines that yielded target products **5a-k**

Entry	R^1	R^2	Product	% LC/MS (254 nm)	LC/MS *m/z* $(M+1)^+$	HRMS *m/z* $(M+1)^+$ (Calc)
1	H	H	5a	43.6	494	
2	4-MeO	H	5b	39.4	554	
3	H	4-MeO	5c	61.2	584	
4	4-CF_3	4-MeO	5d	42.7	720	720.2292 (720.2286)
5	H	4-OH	5e	56.1	542	542.2078 (542.2073)
6	H	3-MeO	5f	5.1	584	584.2525 (584.2544)
7	H	2-Me	5g	<5	536	536.2716 (536.2696)
8	H	3-Cl	5h	<5	596	
9	H	3-F	5i	<5	548	
10	4-MeO	4-MeO	5j	41.8	644	
11	4-CF3	3-Cl	5k	21.0	732	

Scheme 4. Assumed new type of Povarov reaction.



However, extensive one-dimensional (1D) (^1H, ^{13}C, attached proton test (APT)), and two-dimensional (2D) nuclear magnetic resonance (NMR) (heteronuclear single quantum coherence spectroscopy (HSQC) and heteronuclear multiple-bond correlation (HMBC)) analyses did not support the existence of a quinoxaline nucleus within the structure. Therefore, we extended the reactant range to other glyoxals and arylamines while using CAN as the catalyst (Table 3). Compound **5d** was helpful because it could be prepared in 90.3% purity (LC/MS); further, the HRMS data revealed that its molecular formula is $C_{39}H_{31}F_6N_3O_4$. With respect to the determination of its structure, we would like to mention that this compound contains five aromatic rings connected to a scaffold of possibly four carbons, three nitrogens, and an oxygen atom. Hence, we used 1D and 2D NMR spectroscopy to further analyze **5d**.

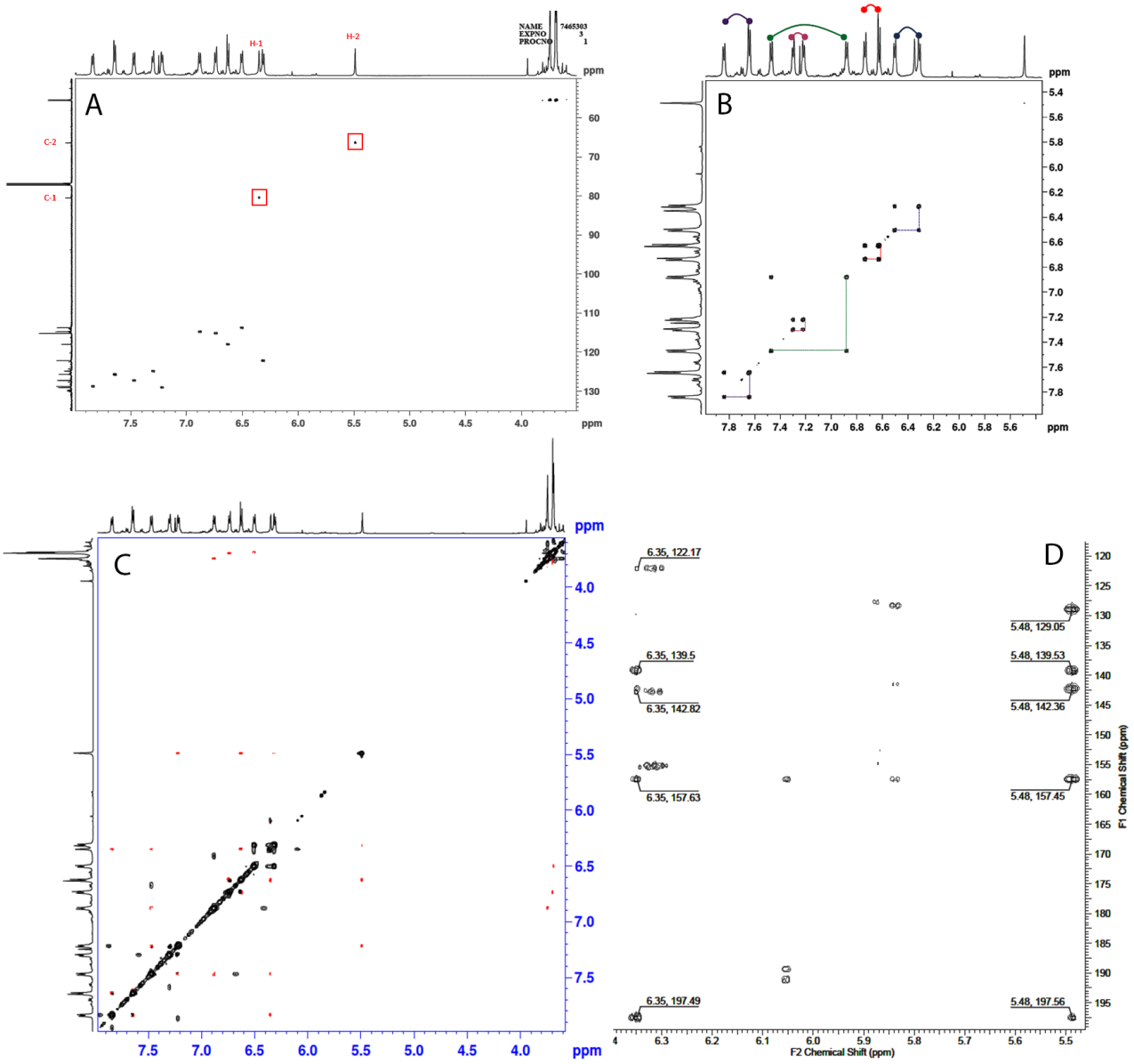


Figure 1. 2D NMR spectra of **5d**: (A) HSQC, (B) COSY, (C) NOESY, and (D) HMBC. The red squares indicate C-1 to H-1 and C-2 to H-2 CH connectivities in the HSQC spectrum. Colors in the COSY spectrum distinguish hydrogens that interact and therefore are located *ortho* to each other, as illustrated in Figure 2. Important HMBC interactions of H-1 (δ_H of 6.35 ppm) and H-2 (δ_H of 5.48 ppm) are marked. Note that interactions between H-1 → δ_c of 122.1 and H-2 → δ_c of 129.0 are strong. All other interactions between H-1 and H-2 are common.

2.2. Determining the structure of 5d using 1D and 2D NMR spectroscopy

The ^{1}H NMR spectrum (Supporting Information Figure SI-3D) of compound **5d** exhibits peaks related to aromatic protons that are separated from each other, and provides key information about atomic connectivity. For instance, all signals from the five benzene rings indicate *para* substitution (A, B proton pattern), indicating that neither the aromatic rings of the glyoxal nor the aniline component were involved in the reaction. Equally important was the observation of a singlet at 6.34 ppm that corresponds to a proton outside the aromatic region (for simplification, this hydrogen is labeled "H-1" and its bonded carbon is labeled "C-1"). Another singlet was observed at 5.48 ppm (labeled "H-2" and its bonded carbon is labeled "C-2"). These two protons helped to elucidate the structure of **5d**. During HSQC analysis (Figure 1A), these two protons exhibited correlated signals at 66.5 and 80.6 ppm respectively, which suggests that two nonaromatic CH moieties are present in the structure of **5d**. The downshifts of the signals related to these two protons indicate that they are attached to carbons that are strongly deshielded by flanking electron-withdrawing groups. Moreover, the correlated spectroscopy (COSY) spectrum of **5d** (Figure 1B) reveals that these two signals are not related to any other peak in the spectrum. Therefore, it is possible that a carbonyl group is attached to the two CH moieties, since the glyoxal reactant contains two carbonyl groups. However, the difference in the

chemical shifts of the peaks corresponding to these two hydrogens (0.86 ppm) as well as the difference between the shifts their corresponding carbons (14.1 ppm) indicate that the neighboring environment consists of chemically different groups. Further, one of them might be a carbonyl and the other might be an imine, which is chemically justified because the reactants contain four active carbonyl groups, which consumed only three *p*-anisidines to form **5d**. In addition, the ^{19}F NMR spectrum exhibited two distinctive signals (integrating equally), indicating that the trifluoromethyl groups of the two glyoxal molecules are present in the compound in two magnetically different aromatic rings (Supporting Information, Figure SI-3G).

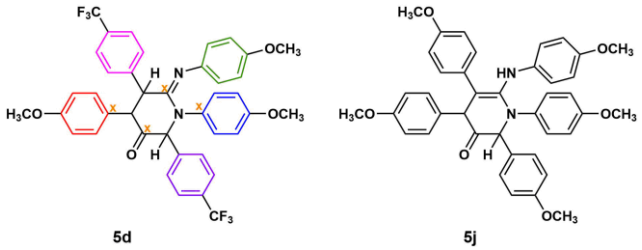
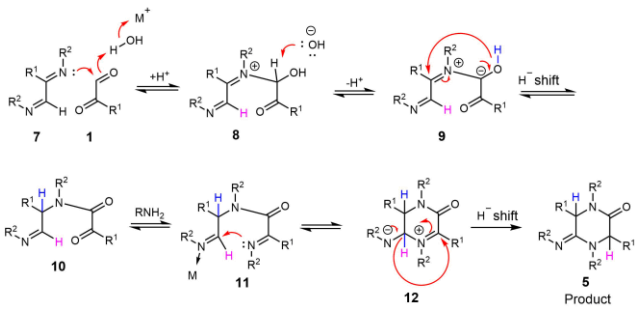


Figure 2. Proposed structures of **5d** and **5j**. The rings in **5d** are colored to reflect the COSY relationships illustrated in Figure 1B. Orange x symbols mark carbon atoms that exhibit HMBC interactions common to H-1 and H-2.

Nuclear Overhauser effect spectroscopy (NOESY) (Figure 1C) confirmed that the three methoxy groups (3.68, 3.69, and 3.74 ppm) are connected *ortho* to aromatic protons with chemical shifts of 6.50, 6.73, and 6.88 ppm, respectively. In addition, on correlating the data from the NOESY and COSY spectra, we confirmed that the protons corresponding to the signals at 6.31, 6.61, and 7.48 ppm are located *meta* to these methoxy groups. Further, H-1 interacts weakly (NOESY) with the proton corresponding to the signal at 7.83 ppm, while H-2 interacts with the proton corresponding to the signal at 7.21 ppm. The latter two aromatic protons are located *meta* to the CF_3 groups in the two phenyl rings that bear them, as per the COSY data. Notably, both H-1 and H-2 exhibit weak interactions (NOESY data) with the proton corresponding to the signal at 6.62 ppm, and this proton is located on one of the three *p*-methoxyphenyl moieties. Moreover, the HMBC spectrum shows that both H-1 and H-2 interact with a set of carbons with signals at 139.5, 142.3, 157.4, and 197.5 ppm (Figure 1D). These four carbons are not attached to any hydrogen, as indicated by ^{13}C APT spectroscopy (Supporting Information Figure SI-3E and F). The carbon corresponding to the signal at 197.6 ppm presumably corresponds to the carbonyl in the structure of **5d**, while the carbon corresponding to the signal at 158.2 ppm is an imine carbon. These HMBC spectral features along with the other spectra data provide crucial insight regarding the existence of a cyclic structure. This cyclic structure means that H-1, H-2, the aromatic rings, and the carbonyl and imine moieties are close enough to facilitate the interactions suggested by NOESY and HMBC spectroscopy. Thus, based on the proposed mechanism and by evaluating all possible structures, we conclude that the structure of **5d** must be that of the piperazinone derivative shown in Figure 2. The pentamethoxy derivative **5j** is a further example of a piperazinone reaction product that was confirmed by 1D and 2D NMR spectroscopy (see Supporting Information Section SI-9). It is notable that **5j** was interpreted to be the enamine tautomer of the imine (Figure 2).

2.3. Proposed reaction mechanism

It is known that imine formation is a reversible process and that, at any moment, the reaction vessel must contain a population of monoimine **6**, di-imine **7,** and unreacted glyoxal **1**. This was confirmed by the formation of **5a** in the reaction illustrated in Scheme 3. Therefore, our proposed mechanism (Scheme 5) starts with the assumption that di-imine **7** reacts with the available starting glyoxal **1**. Thus, when carbonyl-free **7** collides with glyoxal **1**, which is highly electrophilic, in the presence of a Lewis acid catalyst in a head-to-tail manner, the aldehyde probably undergoes nucleophile attack from the nitrogen, resulting in the formation of **8**. This positively charged entity loses a proton to form ylide **9**, triggering a hydride shift that stabilizes the compound by rearranging into intermediate **10**. However, **10**, which is an acyclic oxamide, probably appends an additional ketonic carbonyl and condenses with an extra aniline to form intermediate **11**. It is likely that, regardless of the attenuated nucleophilicity of the nitrogen of the new imine, its proximity to the carbon of the imine on the other side (six-membered cyclic arrangement), along with the presence of the Lewis acid catalyst initiates another cycle involving nucleophilic attack, ylide formation (**12**), and a hydride shift to complete the formation of the final product, **5**.



Scheme 5. Proposed mechanism for the formation of piperazinedione monoamine as the product of the reaction of aniline with phenylglyoxal. M = Lewis Acid.

2.4. Reactant and catalyst scope

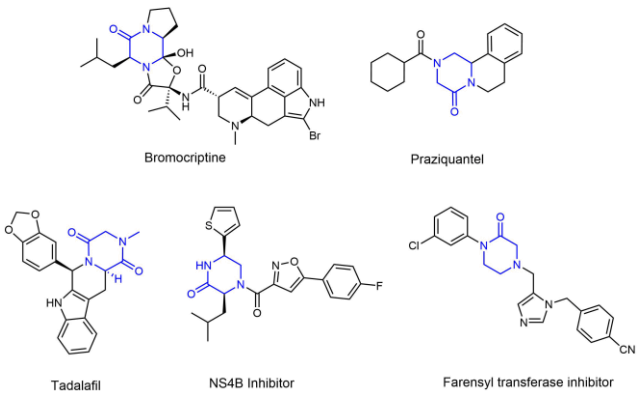
Stirring the reactants in acetonitrile containing 5 mol% ceric ammonium nitrate for 1 h at room temperature

resulted in the highest yield of **5d**. The next-highest yield was achieved using montmorillonite clay. Other conditions investigated, such as heating without a catalyst, and the use of ytterbium triflate or boron trifluoride etherate either yielded no new product or resulted in a low yield. Moreover, CAN appears to act as a Lewis acid catalyst rather than an oxidant[9] because non-oxidant catalysts provided the same product but in lower yields.

The range of arylamines that can be used in this reaction was also investigated. The reaction occurred successfully when arylamines devoid of substituents were used (Entries 1 and 2, Table 3) as well as when substituted with an electron donor, such as a 4-methoxy or 4-hydroxy group (Entries 3, 4, 5, and 11, Table 3). The product yield decreased when a moderately electron-withdrawing group was present at the *meta* position, such as a halogen or methoxy group (Entries 6–10, Table 3). However, the reaction yielded no piperazinone product when the aniline reactant contained an electron-withdrawing group, such as nitro or aminosulfonyl, in the *para* position. Consistent with these results, no product was detected by LC/MS when 2- or 3-aminopyridine was used as the amine. In contrast, the reaction was found not to be very sensitive to the electronic properties of the substituents on the glyoxal. For instance, 3-methoxy, 4-methoxy, and 4-trifluoromethyl phenylglyoxal yielded products in yields comparable to those of phenylglyoxal. However, *ortho* substitution on either the phenylglyoxal component or the aniline component led to a dramatic decrease in product yield. For instance, *o*-methylphenylglyoxal failed to give any desired product while *o*-toluidine had limited success (less than 5%, **5g**, Entry **7**) owing to steric hinderance. It is also worth mentioning that only aromatic amines participate in this reaction. In contrast, aliphatic amines such as 4-methoxy- and 4-fluorobenzylamine failed to produce any piperazine product. This suggests that the ring electrons are involved in stabilizing the intermediates and explains the requirement of a minimal amount of electron density on the aniline ring. It also supports the proposed mechanism (Scheme 5) and explains the existence of the observed intermediates.

Conclusion

Herein, we aimed to report an interesting reaction that produces multi-substituted piperazine derivatives rather than robust reaction methodology. From a practical point of view, this short route to multi-substituted piperazinones should be exploited to obtain medicinally important compounds, given the extensive literature available on this scaffold. For instance, bromocriptine (a dopamine agonist used in the treatment of hyperprolactinemia)[10] and praziquantel[11] (an antiparasitic drug) contain



piperazinone moieties (Figure 3). The piperazinone scaffold and the related 2,5-diketopiperazine compound are used extensively in the design of drug-like compounds with broad biological activities[12], such as tadalafil (a PDE-5 inhibitor used for treating erectile dysfunction)[13], NS4B inhibitors that are active against the hepatitis C virus[14], and farnesyl transferase inhibitors that act against cancers[15] (Figure 3).

Figure 3. Some examples of drugs and biologically active compounds containing piperazinone moieties.

In contrast, the compounds reported in this study were tedious to isolate. The use of silica-gel chromatography was not successful for most products owing to stability issues. Compounds **5d** and **5k** could be isolated in high purity using preparative HPLC. Consequently, we relied on LC/MS data to analyze most of the compounds prepared in this study. Moreover, the products exhibited short half-lives during storage. For instance, compound **5k** was isolated in 100% purity by LC/MS; however, the product MS peak was completely absent after storage at room temperature for 1 week (Supporting Information, Figure SI-10C). Furthermore, the purified reaction products were collected as resins that were unsuitable for crystallographic analysis. Therefore, the value of this work is that it documents an unprecedented reaction pathway that provides highly substituted piperazinones. The reaction can be developed in the future into a readily usable synthesis protocol for producing large-scale arrays for piperazinone and diketopiperazine screening purposes.

Experimental Section

4.1. General Conditions

Melting points were determined using an OptiMelt automated melting point system (Stanford Research Systems, Sunnyvale, CA, USA). NMR spectroscopy was performed on a Bruker AVANCE III 400 system (Bruker, Fällanden, Switzerland). LCMS spectroscopy was performed on an 1260 Infinity LC/MSD system (Agilent Technologies with DAD\ELSD Alltech 3300 and Agilent. The LC\MSD measurements were performed on a G6120B mass spectrometer (Santa Clara, CA, USA) while HRMS was performed using separation and mass spectrometric

detection techniques on an Infinity 1260 UHPLC system (Agilent Technologies, Waldbronn, Germany) coupled to an 6224 Accurate Mass TOF LC/MS system (Agilent Technologies, Singapore). Chromatographic separation was achieved using an Agilent Zorbax C18 column (100mm× 2.1mm, 1.9 µm particle size). Mobile phase A consisted of 0.1% formic acid in water and mobile phase B consisted of 0.1% formic in acetonitrile. The injected volume of the sample solutions was 1 µL. Separation was performed at a constant flow rate of 0.4 mL/min at 40 °C. A linear gradient was started at 5% mobile phase B and ramped to 95% over 6.5 min. Flushing was performed for 1.5 min at 95% mobile phase B. The column was re-equilibrated for 2 min with 5% mobile phase A. Positive-ion mass spectra of the column eluate were recorded in the 100–1500 *m/z* range at a frequency of 9500 transients/s and a detection frequency of 4 GHz. The Agilent ion source was operated using the following conditions: pressure of the nebulizing gas (N_2) was 40 psi and the temperature and flow rate of the drying gas (N_2) were 320 °C and 6 L/min, respectively. The capillary voltage was set to 4 kV, the fragmentor potential to 120 V, and the skimmer potential to 75 V. All solvents and chemicals used were of HPLC grade. The water used was purified using a Millipore water purification system. All chemicals, reagents, and solvents were purified and/or dried in accordance with established methods. Vendors included UORSY (Kiev, Ukraine), Enamine (Kiev, Ukraine), and Merck KGaA (Darmstadt, Germany). Glyoxal derivative **1** was purchased from UORSY (Kiev, Ukraine) and Enamine (Kiev, Ukraine).

4.2. General procedure for synthesis of piperazinone 5

To a stirred solution of the appropriate arylamine derivative, e.g. **2** (4.53 mmol), and the corresponding arylglyoxal (3.02 mmol) in acetonitrile (15 mL) was added CAN (82.78 mg, 0.15 µmol). The mixture was stirred at room temperature overnight. The mixture was then extracted with dichloromethane (2 × 20 mL), and the extract was washed with water and brine and then dried (anhydrous Na_2SO_4). The product was purified by preparative HPLC.

*4.2.1. 1,4-Bis(4-methoxyphenyl)-5-((4-methoxyphenyl)imino)-3,6-bis(4-(trifluoromethyl)phenyl)piperazin-2-one (**5d**).*

The compound was prepared from 4-methoxyaniline (370 mg, 3.00 mmol) and 2-oxo-2-(4-(trifluoromethyl)phenyl)acetaldehyde hydrate (440 mg, 2.00 mmol) and purified using preparatory HPLC, which yielded a resinous residue with an HPLC purity of 90.6% (40 mg, 6.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.68 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 5.48 (s, 1H) 6.30 (d, *J* = 8.50 Hz, 2H), 6.35 (s, 1H), 6.50 (d, *J* = 8.03 Hz, 2H) 6.62 (d, *J* = 9.03 Hz, 2H) 6.73 (d, *J* = 8.53 Hz, 2H) 6.88 (d, *J* = 8.53 Hz, 2H) 7.21 (d, *J* = 7.53 Hz, 2H) 7.29 (d, *J* = 7.53 Hz, 2H) 7.47 (d, *J* = 8.03 Hz, 2H) 7.64 (d, *J* = 8.03 Hz, 2H) 7.83 (d, *J* = 7.53 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 55.4, 55.4, 55.5, 66.4, 80.5, 113.8, 114.7, 114.7, 115.2, 118.1, 122.1, 122.3, 124.3, 124.5, 124.8, 125.6, 125.6, 125.7, 125.75,127.1, 127.7, 128.8, 129.1, 129.7, 129.9, 130.0, 138.5, 139.4, 142.4, 142.9, 155.2, 157.4, 158.2, 197.6; LC/MS (ESI), RT = 1.54 min, *m/z* 720.2 [M + H]+; HRMS (ESI) calculated for $C_{39}H_{31}F_6N_3O_4$ *m/z* 719.2219; found *m/z* 719.2212.

*4.2.2. 1,3,4,6-Tetraphenyl-5-(phenylimino)piperazin-2-one (**5a**)*

This compound was prepared according to the above-described procedure, starting from phenylglyoxal monohydrate (304 mg, 2.0 mmol) and aniline (280 mg, 3.0 mmol). The crude product was purified by column chromatography (silica gel, heptanes–EtOAc, 95:5) to obtain 65 mg (0.16 mg, 5.5%) of **5a** as a yellowish resinous residue, which darkens quickly upon exposure to air at room temperature and slowly if stored at -18 °C in an inert atmosphere. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.63 (s, 1H, corresponding to H-2), 6.42 (d, *J* = 7.8 Hz, 2H), 6.54 (s, 1H, corresponding to H-1), 6.64 (d, *J* = 7.8 Hz, 2H), 6.80 (t, *J* = 6.3 Hz, 2H), 6.95-7.2 (m, 9H), 7.32-7.41 (m, 7H), 7.55 (t, *J* = 7.5 Hz, 2H), (d, *J* = 7.5 Hz, 2H); LC/MS (ESI), RT = 3.75 min, *m/z* 494.6 $[M + H]^+$.

*4.2.3. 1,3,4,6-Tetrakis(4-methoxyphenyl)-5-((4-methoxyphenyl)imino)piperazin-2-one (**5j**)*

This compound was prepared according to the above-mentioned general procedure, starting from 4-methoxyphenylglyoxal monohydrate hydrate (550 mg, 3.02 mmol) and 4-methoxyaniline (558 mg, 4.53 mmol). After purification by HPLC, 42 mg of the desired product (6.5% with 87% purity) was isolated. The product was a soft light-brown residue that darkened quickly upon storage. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.61 (s, 3H), 3.66 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3 H), 3.78 (s, 3H), 3.85 (s, 1H, corresponding to H-2), 6.53 (br. s, 3H) 6.68-6.78 (m, 5H) 6.84 (d, *J* = 8.3 Hz, 2H) 6.91 (d, *J* = 9.3 Hz, 2H) 7.38 (d, *J* =8.3 Hz, 2H) 7.43-7.52 (m, 3H) 7.77 (br. 2H) 7.98-8.11 (m, 3H); LC/MS (ESI), RT = 9.1 min, *m/z* 644.1 $[M + H]^+$.

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Unexpected Synthesis of Multi-substituted Piperazinone Derivatives by Reacting Glyoxals with Anilines

Adv. Synth. Catal. **Year**, *Volume,* Page – Page

Abdelsattar M. E. Omar and Moustafa E. El-Araby*