Novel Synthetic Approach Toward C-Substituted Piperazine Derivatives *via* C-N Bonds Formation of α-Bromoarylethanones and Ethanolamine

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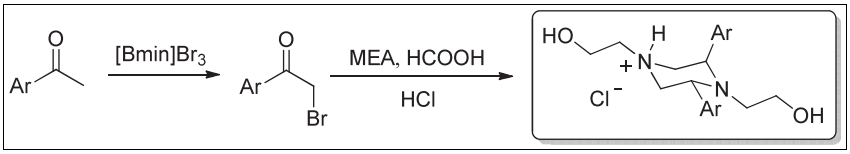

A new method for the synthesis of novel C-substituted piperazine derivatives bearing aryl substituents on 2,6-C positions has been developed by one-pot three-component sequential reaction of α-bromoarylethanones with ethanolamine in the presence of formic acid. The structure of the novel compounds was established by nuclear magnetic resonance (NMR), mass spectrometry (MS), and elemental analysis. In addition, the crystal structure of **4e** was determined by single X-ray crystallography and a possible reaction mechanism was proposed.

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INTRODUCTION

The piperazine ring is a common structural motif and pharmacophore found in a large number of drugs [1–3]. Piperazine derivatives can be used as main structure or substituent of the drugs to obtain the desired pharmacological activity or pharmacokinetic activity, they also can be served as building blocks commonly used in the synthesis of pharmaceutically active substances [4]. The synthesis of piperazine derivatives only bearing nitrogen substituents has received considerable attention, whereas only a comparatively small number of C-substituted piperazine derivatives have been prepared and evaluated for their pharmacological properties [5–10]. In particular, a recent study found that the C-substituent of the piperazine ring in drugs can be modified to reduce the side effects, such as floxacin series drugs with methyl piperazine as side-chain significantly decreased the central nervous system toxicity [11]. So, there is a clear demand for efficient synthetic protocols to construct the C-substituted piperazine derivatives.

In the course of our studies on the C-N bonds formation based on α-bromoalkylaryl ketones [12–14], a new route for preparing 4-bis(2-hydroxyethyl)-2,6-bisaryl piperazines has been developed. The synthesis of the title compounds was achieved by α-bromoarylethanones reacted with ethanolamine (MEA) in the presence of formic acid (HCOOH) in *N*-methyl-2-pyrrolidone (NMP) solution (Scheme 1).

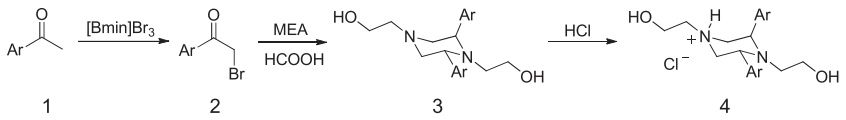
RESULTS AND DISCUSSION

The α-bromination of arylethanones (**1**) was accomplished in high isolated yields under solvent-free condition and in short reaction times using 1-butyl-3-methyllimidazolium tribromide ([Bmin]Br_3) [15] as the bromine source (Table 1). The bromination proceeds to take place at the carbon atom activated by the C═O group with high selectivity. Following isolation of the brominated products, the low viscosity, high density trihalide-based [Bmin]Br_3 ionic liquid was easily recovered and can be reused with minimal loss.

Then one-pot three-component sequential reaction of the bromides (**2**) with MEA and HCOOH was taken in polar aprotic solvent (NMP) [16] to give the title C-substituted piperazine derivatives. Finally, since the title piperazine derivatives in the form of free amino base are readily polymerizable, the obtained products were quickly converted to its hydrochloride salts in ethanol solution of anhydrous HCl, and then the products were separated and purified by column chromatography. The progress of the reaction was monitored by thin layer chromatography (TLC) and the yields reported were estimated on the basis of isolated yields (Table 2). The reaction conditions were not optimized yet. At the beginning, we tried to isolate the crude products after acid and then base extraction [17], but the yields of the desired products were unacceptable (less than 5%).

Many reagents for nucleophilic substitution of α-bromoketones to form C-N bonds have been developed [18–20]. Whereas there has been no reports on MEA as a nucleophile

Scheme 1



Ar	
a C_6H_5;	b 4-MeC_6H_4;
c 4-EtC_6H_4;	d 4-$MeOC_6H_4$;
e 2,4-diCl-5-FC_6H_2;	f 6-$MeOC_{10}H_6$;
g 2-Cl-4-(4-ClC_6H_4O)C_6H_3.	

agent of α-bromoketones. However, MEA is a primary amine and contains an active hydroxyl group, so there is a synthetic difficulty in the reaction of α-bromoketones with MEA to form a single product, the pathway will meet with major difficulties in terms of side reactions such as hydrogen halide elimination, Williamson reaction, oxidation reaction, etc. We have traced the oxidation product 2-(2,4-dichloro-5-fluorophenyl)-2-oxoacetaldehyde [21] in this reaction. Therefore, the finial C-substituted piperazine derivatives were obtained in a moderate yields.

Scheme 2 shows a plausible reaction mechanism of the sequential reaction. The piperazine ring system may be effected in two ways: (I) Firstly, reaction of MEA with α-bromoarylethanones produced the corresponding substituted aminoketones (A). At the same time, addition of carbonyl group with primary amine (MEA) followed by dehydration also afforded the intermediary imines (B), subsequent reductive amination by HCOOH *via* Leuckart-Wallach reaction [22] leads to C. Next, a self-consistent sequence nucleophilic substitution between the aminoketones and C formed the key intermediates D. Then D undergoes an intramolecular cyclization to give the 2,2′-(2-hydroxy-2,6-bisarylpiperazine-1,4-diyl) diethanols (E). E, by losing a water molecule, forms a cyclic Schiff base intermediate F. Subsequent reduction by HCOOH leads to the desired product piperazine derivatives. (II) Initially, α-bromoarylethanones straightforward nucleophilicly attacked by the MEA to afford the aminoketones. Consequently, the resulting aminoketones (secondary amine) as a nucleophile, attacked the starting material α-bromoarylethanones again to give the key intermediates D. Following, similarly to route I, the desired products were obtained by the intramolecular cyclization.

The structure and stereochemical properties of the representative compound **4e**, 2,2′-(2,6-bis(2,4-dichloro-5-fluorophenyl)piperazine-1,4-diyl)diethanol hydrochloride was investigated by X-ray diffraction. Colorless crystals suitable for X-ray diffraction analysis were grown by slow evaporation of ethanol. The molecular structure of **4e** is illustrated in Figure1. The piperazine ring is a distorted chair somewhat flattened at N2 and sharpened at N1. The N atoms of the piperazine ring and the oxygen atoms of the hydroxyl group act as hydrogen-bond donors to the Cl atoms of the hydrochloride formed intramolecular and intermolecular hydrongen bonds. The combination of N—H···Cl and O—H···Cl hydrogen bonds generates a cyclic centrosymmetric R_4^2 (14) [23] aggregates of two molecules (Fig. 2).

CONCLUSIONS

To summarize, this is the first report, to the best of our knowledge, on the synthesis of pharmaceutically important C-substituted piperazine derivatives by C-N bonds formation of α-bromo-arylethanones and MEA. The title C-substituted piperazines have novel structural features, and the two active hydroxyl groups can be derived into other more complicated compounds. Currently, work is in progress to further expand the scope of this method.

Table 1

Results of the bromination of arylethanones (**1**) by [Bmin]Br_3.

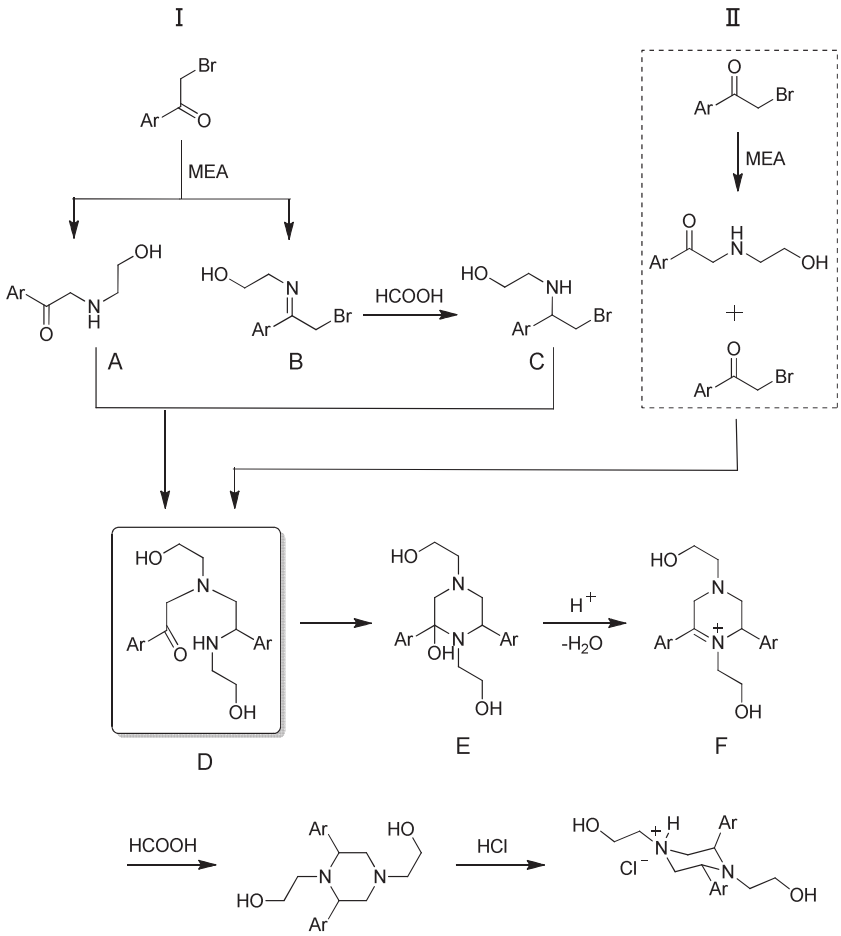
Entry	Ar	Time (min)	Yield (%)
a	C_6H_5	10	90.1
b	4-MeC_6H_4	6	90.8
c	4-EtC_6H_4	5	90.2
d	4-$MeOC_6H_4$	8	92.6
e	2,4-diCl-5-FC_6H_2	16	83.2
f	6-$MeOC_{10}H_6$	10	93.6
g	2-Cl-4-(4-ClC_6H_4O)C_6H_3	12	87.8

Table 2

Synthesis of 4-bis(2-hydroxyethyl)-2,6-bisaryl piperazine hydrochlorides (**4**).

Entry	Ar	Time (h)	Yield (%)	M.p. (°C)
a	C_6H_5	12	35.2	265.2.266.7
b	4-MeC_6H_4	16	32.1	271.6.272.4
c	4-EtC_6H_4	16	34.8	270.5.271.5
d	4-$MeOC_6H_4$	18	30.5	269.3.270.5
e	2,4-diCl-5-FC_6H_2	20	35.7	283.6.284.6
f	6-$MeOC_{10}H_6$	20	38.6	225.6.227.3
g	2-Cl-4-(4-ClC_6H_4O)C_6H_3	24	25.8	254.5.255.4

Scheme 2. Possible mechanism for the synthesis of C-substituted piperazine derivatives.



EXPERIMENTAL

All melting points were measured on an X-4 electrothermal digital melting point apparatus and were uncorrected; NMR spectra were recorded on a Bruker advance instrument, chemical shifts (δ) are expressed in ppm; electro-spray ionization mass spectrometry (ESI-MS) were recorded on a Finngan LCQ LC-MS spectrometer; element analyses were performed on a Perkin–Elmer 240 CHN analyzer; TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light or iodine; the IUPAC names were obtained using the software ChemDraw Ultra®, version 12.0. Every starting material was obtained from commercial suppliers and was purified according to the literature procedures.

General experimental procedure for the preparation of 4a–4g. α-Bromoarylethanones (0.04 mol) was dissolved in 50 mL NMP, MEA (0.16 mol) was added dropwise at room temperature. The resulting solution was stirred for 30 min, then warmed to 60°C and stirred for further 1 h. After cooled down to room temperature, 7.5 mL HCOOH (90.5%) was added, the mixture was stirred and heated to reflux. After the reaction finished, an excess of 80 mL water was added, the mixture was extracted five times with 50 mL CH_2Cl_2. The extracts were combined and dried over anhydrous Na_2SO_4. The CH_2Cl_2 was removed by distillation, and then the free amino base crude product was dissolved in ethanol, anhydrous HCl was passed through slowly. Finally, the ethanol was concentrated and the residue were separated and purified by column chromatography to give the title compounds **4a–4g**.

2,2′-(2,6-diphenylpiperazine-1,4-diyl)diethanol hydrochloride (4a). ^{1}H-NMR (CD_3SOCD_3+D_2O, 400 MHz) δ: 2.70–2.81 (m, 4H, 2× NCH_2), 3.39 (t, J = 12.0 Hz, 2H, OCH_2), 3.46–3.66 (m, 6H, piperazine ring 3,5-H, OCH_2), 4.53 (d, J = 11.6 Hz, 2H, piperazine ring 2,6-H), 7.49–7.62 (m, 10H, benzene ring H). ^{13}C NMR (CD_3SOCD_3+D_2O, 100 MHz) δ: 54.4, 54.6, 55.3, 58.3, 64.2, 127.1, 128.3, 129.2, 138.3; ESI-MS (m/z): 326 (M^+-HCl), 308 (M^+-HCl-H_2O); Analysis calculated for $C_{20}H_{27}ClN_2O_2$: C, 66.19; H, 7.50; N, 7.72. Found: C, 66.23; H, 7.42; N, 7.83.

2,2′-(2,6-di-p-tolylpiperazine-1,4-diyl)diethanol hydrochloride (4b). ^{1}H-NMR (CD_3SOCD_3+D_2O, 400 MHz) δ: 2.36 (s, 6H, 2× CH_3), 2.83–2.87 (m, 4H, 2× NCH_2), 3.50–3.61 (m,6H, piperazine ring 3,5-Ha, 2× OCH_2), 3.71, 3.74 (dd, J = 10.0 Hz, J = 2.8 Hz, 2H, piperazine ring 3,5-He), 4.68 (d, J = 10.0 Hz, 2H, piperazine ring 2,6-H), 7.35 (d, J = 8.0 Hz, 4H, 2× benzene ring 2,6-H), 7.53 (d, J = 8.0 Hz, 4H, 2× benzene ring 3,5-H); ^{13}C-NMR (CD_3SOCD_3+D_2O, 100 MHz) δ: 20.8, 54.1, 54.9, 55.1, 56.1, 63.9, 128.8, 130.2, 140.2; ESI-MS (*m*/*z*): 354 (M^+-HCl), 336 (M^+-HCl-H_2O). Analysis calculated for $C_{22}H_{31}ClN_2O_2$: C, 67.59; H, 7.99; N, 7.17. Found: C, 67.41; H, 8.05; N, 7.19.

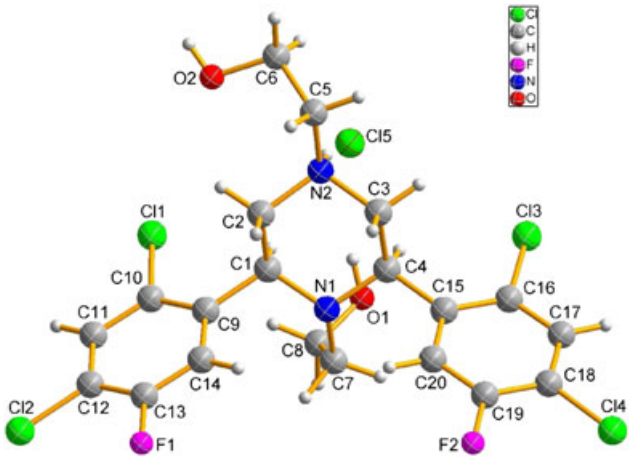


Figure 1. X-ray structure of 4e, with displacement ellipsoids drawn at the 30% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2,2′-(2,6-bis(4-ethylphenyl)piperazine-1,4-diyl)diethanol hydrochloride (4c). ^{1}H-NMR (CD_3SOCD_3+D_2O, 400 MHz) δ: 1.21 (t, *J* = 7.6 Hz, 6H, 2× CH_3), 2.63–2.72 (m, 6H, 1-NCH_2, 2× CH_2), 2.77–2.83 (m, 2H, 4-$^+NCH_2$), 3.36 (t, *J* = 12.0 Hz, 2H, OCH_2), 3.45–3.62 (m, 6H, OCH_2, piperazine ring 3,5-H), 4.66 (d, *J* = 10.8 Hz, 2H, piperazine ring 2,6-H), 7.36 (d, *J* = 8.0 Hz, 4H, 2× benzene ring 2,6-H), 7.50 (d, *J* = 8.0 Hz, 4H, 2× benzene ring 3,5-H); ^{13}C-NMR (CD_3SOCD_3+D_2O, 100 MHz) δ: 14.6, 26.6, 54.6, 54.7, 55.8, 58.2, 64.3, 127.3, 129.7, 141.3; ESI-MS (*m/z*): 382 (M^+-HCl), 364 (M^+-HCl-H_2O). Analysis calculated for $C_{24}H_{35}ClN_2O_2$: C, 68.80; H, 8.42; N, 6.69. Found: C, 68.87; H, 8.35; N, 6.60.

2,2′-(2,6-bis(4-methoxyphenyl)piperazine-1,4-diyl)diethanol hydrochloride (4d). ^{1}H-NMR (CD_3SOCD_3+D_2O, 400 MHz) δ: 2.78–2.87 (m, 4H, 2× NCH_2), 3.34 (t, *J* = 12.0 Hz, 2H, OCH_2), 3.47–3.64 (m, 6H, piperazine ring 3,5-H, OCH_2), 3.78 (s, 6H, 2× OCH_3), 4.45 (d, *J* = 11.6 Hz, 2H, piperazine ring 2,6-H), 7.07 (d, *J* = 8.4 Hz, 4H, 2× benzene ring 3,5-H), 7.52 (d, *J* = 8.4 Hz, 4H, 2× benzene ring 2,6-H); ^{13}C-NMR (CD_3SOCD_3+D_2O, 100 MHz) δ: 52.7, 54.6, 54.9, 56.4, 57.2, 63.7, 115.0, 128.5, 129.8, 158.3; ESI-MS (*m/z*): 386 (M^+-HCl), 368 (M^+-HCl-H_2O). Analysis calculated for $C_{22}H_{31}ClN_2O_4$: C, 62.48; H, 7.39; N, 6.62. Found: C, 62.52; H, 7.30; N, 6.60.

2,2′-(2,6-bis(2,4-dichloro-5-fluorophenyl)piperazine-1,4-diyl)diethanol hydrochloride (4e). ^{1}H-NMR (CD_3SOCD_3, 400 MHz) δ: 2.27 (t, *J* = 6.8 Hz, 2H, 1-NCH_2), 3.14–3.18 (m, 4H, 4-$^+NCH_2$, piperazine ring 3,5-Ha), 3.43–3.50 (m, 4H, piperazine ring 3,5-He, OCH_2), 3.76 (t, *J* = 6.8 Hz, 2H, OCH_2), 4.96 (d, *J* = 11.2 Hz, 2H, piperazine ring 2,6-H), 5.40 (s, 1H, OH), 7.94 (d, *J* = 6.0 Hz, 2H, 2× benzene ring 6-H), 8.02 (d, *J* = 10.0 Hz, 2H, 2× benzene ring 3-H), 11.07 (brs, 1H, $^+$NH); ^{13}C-NMR (CD_3SOCD_3+D_2O, 100 MHz) δ: 54.2, 57.6, 59.5, 59.7, 64.7, 112.5, 119.2, 127.9, 132.5, 137.7, 161.4; ESI-MS (*m/z*): 500 (M^++2-HCl), 498 (M^+-HCl), 497(M^+-HCl-H). Analysis calculated for $C_{20}H_{21}Cl_5F_2N_2$ O_2: C, 44.76; H, 3.94; N, 5.22. Found: C, 44.82; H, 3.88; N, 5.31.

2,2′-(2,6-bis(6-methoxynaphthalen-2-yl)piperazine-1,4-diyl)diethanol hydrochloride (4f). ^{1}H-NMR (CD_3SOCD_3+D_2O, 400 MHz) δ: 2.27–2.34, 2.40–2.45 (m, 4H, 2× NCH_2), 2.88–3.09 (m, 4H, piperazine ring 3,5-H), 3.33–3.61 (m, 4H, 2× OCH_2), 3.86 (s, 6H, 2× OCH_3), 3.98 (d, *J* = 9.2 Hz, 2H, piperazine ring 2,6-H), 7.14–7.87 (m, 12H, 2× naphthalene ring H); ^{13}C-NMR (CD_3SOCD_3+D_2O, 100 MHz) δ: 54.3, 56.7, 58.2, 59.3, 60.2, 64.7, 105.2, 118.7, 125.6, 126.4, 126.9, 128.5, 129.2, 133.3, 136.4, 156.8; ESI-MS (*m/z*): 524 (M^++2), 523 (M^++1), 522 (M^+). Analysis calculated for $C_{30}H_{35}ClN_2O_4$: C, 68.89; H, 6.74; N, 5.36. Found: C, 68.95; H, 6.80; N, 5.40.

2,2′-(2,6-bis(2-chloro-4-(4-chlorophenoxy)phenyl)piperazine-1,4-diyl)diethanol hydrochloride (4g). ^{1}H-NMR (CD_3SOCD_3+ D_2O, 400 MHz) δ: 2.67–2.82 (m, 4H, 2× NCH_2), 3.30 (t, *J* = 12.0 Hz, 2H, OCH_2), 3.45–3.61 (m, 6H, piperazine ring 3,5-H, OCH_2), 4.85 (d, *J* = 12.0 Hz, 2H, piperazine ring 2,6-H), 7.14–7.90 (m, 14H, benzene ring H); ^{13}C-NMR (CD_3SOCD_3+D_2O, 100 MHz) δ: 54.2, 56.5, 57.8, 59.3, 60.2, 65.0, 117.3, 118.6, 119.7, 127.6, 129.4, 129.9, 130.5, 133.4, 155.3, 160.1; ESI-MS (*m/z*): 648 (M^++2-HCl), 646 (M^+-HCl). Analysis calculated for $C_{32}H_{31}Cl_5N_2O_4$: C, 56.12; H, 4.56; N, 4.09. Found: C, 56.23; H, 4.60; N, 4.01.

Selected crystallographic data for compound 4e. $C_{20}H_{21}Cl_5F_2N_2O_2$, *M* = 536.64, 0.47 × 0.21× 0.20 mm^3, monoclinic, space group: $P2_1/c$, *a* = 12.2228(6), *b* = 7.0055(4),

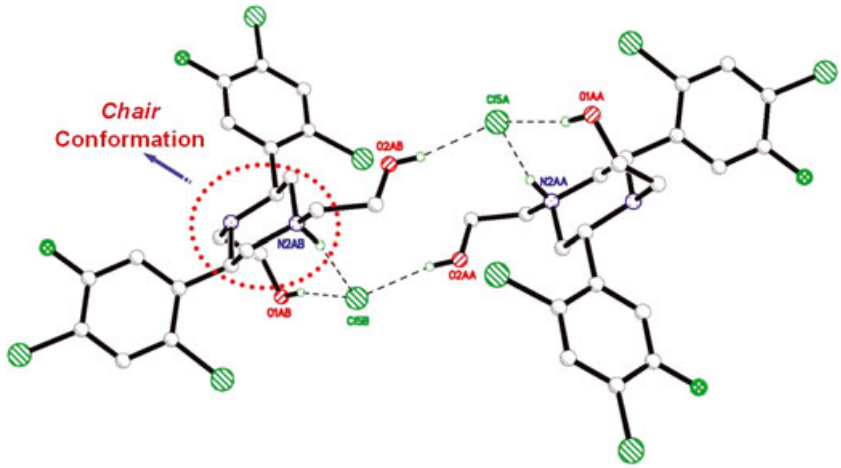


Figure 2. A perspective view of the crystal packing along the *c*-axis. H atoms bonded to C atoms have been omitted for clarity. Dashed lines indicate hydrogen bonds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

c = 27.7206(15) Å, β = 104.1140(10)°, V = 2302.0(2) Å^3, Z = 4, density$_{calcd}$ = 1.548 mg/m^3, F(000) = 1096, intensity data of 5001 reflections were collected in the range $-15 \leq h \leq 7$, $-8 \leq k \leq 8$, $-30 \leq l \leq 35$, GOF = 0.625, $1.51 < \theta < 27.11°$, Final R indices [$I > 2\sigma(I)$] R_1 = 0.0423, wR_2 = 0.1124, R indices (all data) R_1 = 0.0640, wR_2 = 0.1377, Largest diff. peak and hole: 0.432 and −0.281 e Å^{-3}. CCDC 831723 contains the supplementary crystallographic data for this article. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CBZ IEZ, UK. Facsimile (44) 01223 336 033 deposit@ccdc.cam.ac.uk or http//www.ccdc.com.ac.uk/deposit.

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[17] After the reaction finished, 10% aqueous HCl solution (50 mL) was added, and the mixture was washed three with CH_2Cl_2 (30 mL) to remove the neutral compounds. After addition of a cold 30% aqueous NaOH solution (30 mL) to the aqueous layer, the mixture was extracted six times with CH_2Cl_2 (50 mL). The extracts were combined and dried over anhydrous Na_2SO_4. The CH_2Cl_2 was removed by distillation, and the residue was dissolved in ethanol, anhydrous HCl was passed through slowly. Finally, ethanol was concentrated and the crystals were collected on a filter to give the title compounds.

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[21] ^{1}H-NMR data for 2-(2,4-dichloro-5-fluorophenyl)-2-oxoacetaldehyde ($CDCl_3$, 400 MHz) δ: 7.59 (*d*, *J* = 6.4 Hz, 1H, benzene ring 6-H), 7.85 (*d*, *J* = 9.2 Hz, 1H, benzene ring 3-H), 9.88–10.47 (m, 1H, CHO).

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