Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Microwave assisted rapid synthesis of phenoxazines and benzopyridoxazines

Kavitha Anchan , Nagaswarupa H. Puttappa , Baburajan Poongavanam & Sujit Kumar Sarkar

To cite this article: Kavitha Anchan , Nagaswarupa H. Puttappa , Baburajan Poongavanam & Sujit Kumar Sarkar (2020): Microwave assisted rapid synthesis of phenoxazines and benzopyridoxazines, Synthetic Communications, DOI: 10.1080/00397911.2020.1849723

To link to this article: https://doi.org/10.1080/00397911.2020.1849723

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2020.1849723

Taylor & Francis
Taylor & Francis Group

Microwave assisted rapid synthesis of phenoxazines and benzopyridoxazines

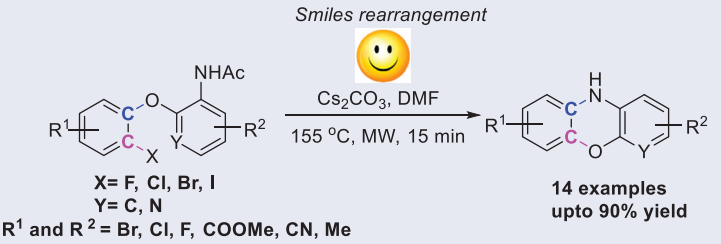
Kavitha Anchan[a,b], Nagaswarupa H. Puttappa[a,c], Baburajan Poongavanam[b], and Sujit Kumar Sarkar[b]

[a]Research and Development Centre, Bharathiar University, Coimbatore, India; [b]Discovery Chemistry, Syngene International Limited, Bangalore, India; [c]Department of studies in chemistry, Davangere University, Davangere, India

ABSTRACT

A facile protocol for the synthesis of phenoxazines and benzopyridoxazines by Smiles rearrangement have been demonstrated in short reaction time under microwave irradiation. The control experiments suggest that a reaction proceeds through Smiles rearrangement followed S_NAr ring closure by *in situ* cascade process. In our present work, both the electron donating and electron withdrawing groups were tolerant and provided a corresponding phenoxazine/benzopyridoxazine in good to moderate yields.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 26 July 2020

KEYWORDS
Benzopyridoxazines; microwave irradiation; phenoxazines; smiles rearrangement; SNAr cyclization

Introduction

Phenoxazines and benzopyridoxazines are 6/6/6 fused tricyclic heterocycles which are gaining attention of researchers as they exhibit biological properties and are used as building blocks in medicinal chemistry.[1] *N*-substituted analogues of phenoxazines are less toxic modulators of multidrug resistant (MDR) in cancer cells.[2] Derivatives of phenoxazines have been used as visible light absorbing reducing organic photoredox catalysts (PCs).[3] Owing to their photophysical properties,[4] they have been applied as dyes in dye-sensitized solar cells[5] and chemosensors.[6] A block copolymer comprised of polyfluorene (PF) and polytriarylamine (PTAA) functionalized with substituted phenoxazines are finding a place in electroluminescent applications.[7]

CONTACT Baburajan Poongavanam baburajan29@gmail.com; Nagaswarupa H. Puttappa nagaswarupa77@gmail.com
Discovery Chemistry, Syngene International Limited, Bangalore 560099, India.

Supplemental data for this article can be accessed on the publisher's web.

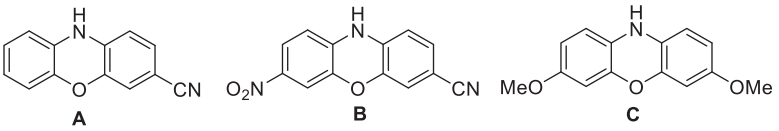


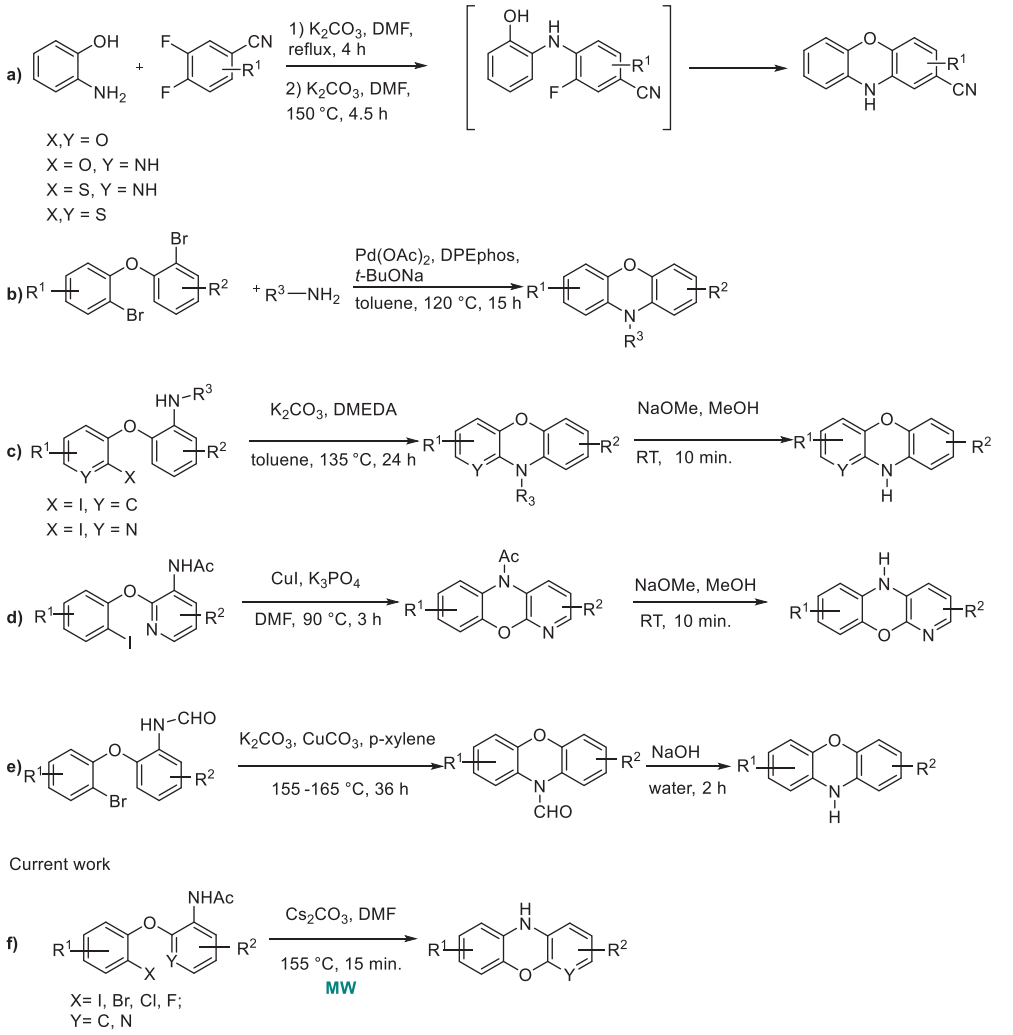
Figure 1. Structures of few phenoxazine containing RTAs.

Block copolymers with phenoxazine cores help in improving the efficiency of polymer light emitting diodes (PLEDs).[8] Recently, Pratt and his group reported that phenoxazines have considerably greater reactivity (by up to 2 orders of magnitude) when compared to diphenylamine and phenothiazine RTAs (Figure 1) which are commonly used as antioxidants.[9] General methods to prepare phenoxazines involve Smiles rearrangements, transition metal-catalyzed coupling reactions and nucleophilic substitution reactions. Among these, Smiles rearrangement reactions offer high degree of diversity to synthesize complex molecules.[10] Phenothiazines which are one of the privileged scaffolds in medicinal chemistry are generally prepared by using a base mediated via Smiles rearrangements of *N*-(2-((2-nitrophenyl)thio)phenyl)acetamide/*N*-(2-((2-bromophenyl)thio)phenyl)acetamide.[11] Unlike phenothiazines, the phenoxazines were less explored. In Scheme 1, some of the protocols to synthesize phenoxazines and benzopyridoxazines are depicted. Eastmond et al. reported a base-catalyzed synthesis of cyanophenoxazines by cyano activated fluoro displacement reactions via Smiles rearrangement (Scheme 1a).[12] Yang et al. developed a palladium catalyzed double *N*-arylation using di(2-bromoaryl)ethers and primary amines (Scheme 1b).[13] Bolm and his group reported a transition metal-free direct *N*-arylation to synthesize phenoxazines/benzopyridoxazines by intramolecular cyclization for Iodo precursor (Scheme 1c).[14] However, the reaction was unsuccessful with bromo precursor. Pratt et al. reported copper-mediated synthesis of phenoxazines/benzopyridoxazines from Iodo diphenyl ethers (Scheme 1d).[15] Eregowda et al. reported the synthesis of phenoxazines from bromo diphenyl ethers under Ullmann condition at higher temperature for longer duration (Scheme 1e).[16] Recently, Olofsson et al. reported the metal-free synthesis of *N*-acetylphenoxazines by *o*-arylation of phenol with unsymmetrical diaryliodonium salt followed by intramolecular *N*-arylation.[17] All these method of synthesis involve either activated substrate (EWG) or transition metal-mediated conditions are required with limited substrate scopes. Also, de-protection (acetyl, formyl) steps are required to get the free NH-phenoxazines. Thus, developing a metal free and general route to synthesize the skeleton of free NH- phenoxazines and benzopyridoxazines derivatives directly are useful to further derivatize the various *N*-substituted analogues.

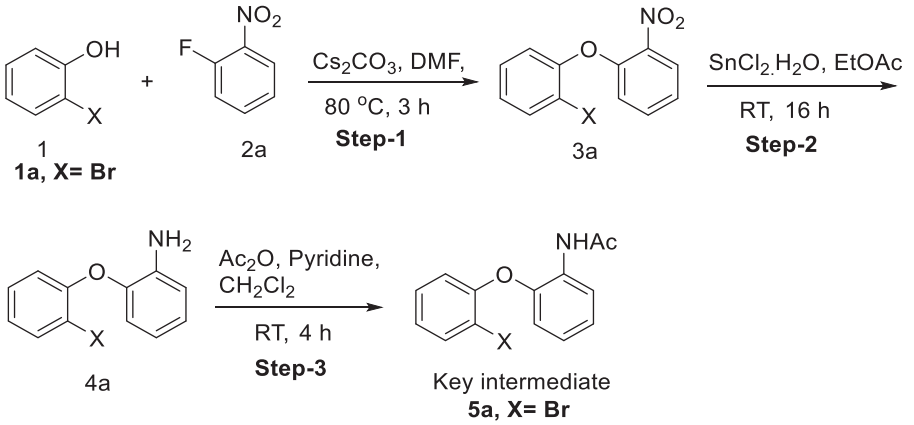
Our present work (Scheme 1f) involves microwave promoted rapid short time synthesis of phenoxazines/benzopyridoxazines derivatives starting from a commercially available starting material or easily synthesized precursors.

Results and discussion

Initial attempts to develop the methodology of phenoxazine and benzopyridoxazine was carried out with *N*-acetyl diphenyl ether (compound 5a), which could be easily synthesized in a 3 step protocol starting from 1-fluoro-2-nitrobenzene with 2-bromo phenol as shown in Scheme 2.[14] Base mediated nucleophilic displacement of compound **2a** with compound **1a** resulted in 1-bromo-2-(2-nitrophenoxy)benzene **3a** with 89% yield

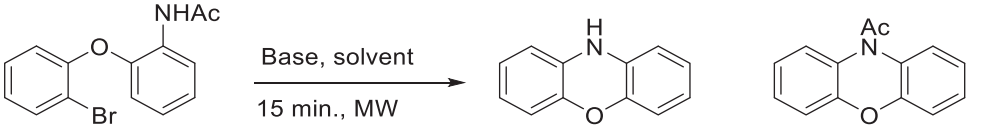


Scheme 1. Synthesis of phenoxazines and benzopyridoxazines.



Scheme 2. Synthesis of key intermediate *N*-(2-(2-bromophenoxy)phenyl)acetamide (**5a**).

Table 1. Optimization of reaction conditions for the synthesis of phenoxazine.



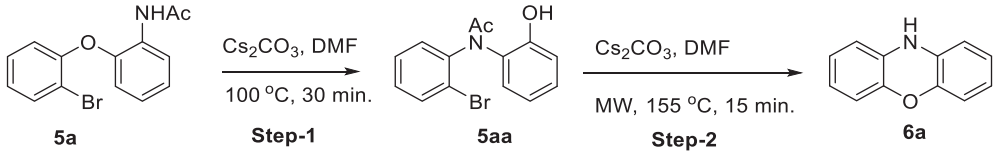
5a **6a** **6aa**

Entry	Base	Solvent	Temp. [°C]	Time [min]	Yield (%)[a] **(6a:6aa)**
1	Na_2CO_3	DMF	130	30	17:07
2	Na_2CO_3	DMF	130	60	12:0
3	Na_2CO_3	DMF	100	30	traces
4	Na_2CO_3	DMF	150	30	28:0
5	Na_2CO_3	DMSO	150	30	11:0
6	Na_2CO_3	NMP	130	30	09:0
7	Na_2CO_3	Toluene	130	30	00-0
8	Na_2CO_3	Xylene	150	30	00-0
9	K_2CO_3	DMF	150	30	32:0
10	Cs_2CO_3	DMF	150	30	67:0
11	Cs_2CO_3	DMF	155	15	83:0
12	Cs_2CO_3	DMF	155	5	48:27[b]

Reaction condition: **5a** (0.5 mmol), base (1.0 mmol), 2 mL solvent in MW heating. [a]Yield of isolated products by column chromatography. [b]0.5 mmol (1.0 equiv.) of base was used.

(step-1). Which then taken for nitro reduction under $SnCl_2{\cdot}H_2O$ condition to provide the quantitative amine intermediate **4a** (step-2). We attempted the direct intra molecular cyclization of amine **4a** to get the phenoxazine **6a** by using different bases in different solvents at 100–180 °C, were unsuccessful. As we have observed either unreacted starting material or decomposed starting material. Further to favor cyclization over the Smiles rearrangement,[18] we converted free amine **4a** to the corresponding *N*-acetyl diphenyl ether **5a** by acetylation (step-3).

Optimization of the cyclization reaction was carried out using *N*-(2-(2-bromophenoxy)phenyl)acetamide **5a** as model substrate to get 10*H*-phenoxazine **6a** or *N*-acetyl-phenoxazine **6aa**. First, we chose conventional thermal heating condition (80 °C to 160 °C, 1–14 h) and observed traces of 10*H*-phenoxazine **6a** (<10% isolated yield) and many unidentified products. Further attempts to increase the yield of the phenoxazine **6a** were unsuccessful (data not shown). Then, we switched to microwave (MW) heating as the high temperature reactions can be carried out safely in a microwave reactor. The obtained results are shown in Table 1. To our delight, when we used Na_2CO_3 as a base in DMF under microwave irradiation at 130 °C for 30 minutes (Table 1, entry 1) we obtained 17% of 10*H*-phenoxazine **6a** and 7% of *N*-acetyl phenoxazine **6aa** as product by isolated yield. Reduced temperature and longer reaction time (Table 1, entries 2 and 3) affected the yield of the **6a** negatively. Increasing the reaction temperature to 150 °C, resulted in slightly increased yield of **6a** up to 28% (Table 1, entry 4). We screened multiple bases and solvents to optimize the yield as shown in Table 1, we found that Cs_2CO_3 (2.0 equiv.) base and DMF as solvent under shorter duration (MW, 15 min at 155 °C) resulted in excellent yield (83%) of 10*H*-phenoxazine **6a** (Table 1, entry 11). Further varying any of the parameters didn't increase the yield of **6a.** When the reaction was performed with 1.0 equiv. of Cs_2CO_3 (Table 1, entry 12) we obtained 48% of **6a**



Scheme 3. Control experiment to trap the Smiles product (**5aa**).

and 27% **6aa**. This result showed that the reaction required 2.0 equiv. of base in order to get the acetyl cleaved free NH phenoxazine **6a** as single product.

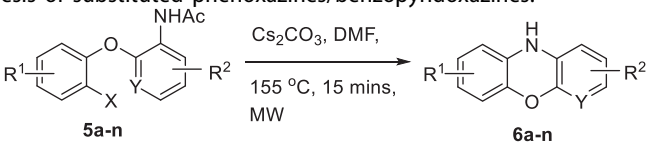
Although Smiles rearrangements of diaryl ethers bearing secondary amides have been previously reported,[19] the control experiment was conducted to trap the rearranged intermediate diphenyl amine **5aa** (shown in Scheme 3). Since our optimized reaction condition (Table 1, entry 11) gave major desired phenoxazine **6a**, we just reduced the reaction duration to 5 min. and identified the Smiles rearranged product **5aa** was formed in 22% along with 34% of cyclized phenoxazine **6a**. When the reaction was carried out at 100 °C for 15 min under microwave conditions we obtained the Smiles rearranged product *N*-(2-bromophenyl)-*N*-(2-hydroxyphenyl)acetamide **5aa** in 78% yield (Scheme 3, step-1). The isolated **5aa** was characterized by ^{1}H-NMR and ^{13}C-NMR.

Further, the *N*-(2-bromophenyl)-*N*-(2-hydroxyphenyl)acetamide **5aa** was exposed to the standard reaction condition (Scheme 3, step-2) resulting in the formation of phenoxazine **6a** in slightly lower yield (68%). Based on this experiment and observation, we found that the reaction proceeds firstly Smiles rearrangement and forms the diphenyl amine intermediate **5aa** which then undergoes C-O bond formation by intramolecular nucleophilic substitution (S_NAr), subsequently the deacetylation happens under base and high temperature condition to produces the 10*H*-phenoxazine **6a**.

As shown in Scheme 4, in order to find the feasibility of the same cyclization to get 10*H*-phenoxazine **6a**, the aryloxy acetanilides having different leaving groups X = Cl (**5a′**), F (**5a″**) and I (**5a‴**) were synthesized (following the synthetic sequence in Scheme 2) and attempted with the optimized reaction condition (Table 1, entry-11). When X = Cl (**5a'**) we obtained 85% of product and when X = F (**5a″**) we obtained 90% isolated yield of 10*H*-phenoxazine **6a**. Similarly, the poor leaving group X = I (**5a‴**) also cyclized and yielded 74% yield of **6a**. With the optimized condition in hand, we set out to investigate the scope of the various substituted key intermediates of aryloxy acetanilides having different leaving groups (Br, Cl, F and I) and functional groups like (COOMe, CN, Me, Cl, Br, F) were synthesized (**6a–6n**) starting with the corresponding phenol derivatives (**1a–1n**) and nitro derivatives (**2a–2n**) by following the Scheme 2 reaction sequence.[14] The results obtained are shown in Table 2. As expected, the cyclization worked well with the ortho, meta and para substituted analogues (**6a–6n**). Moreover, it indicates that the efficiency of the reaction toward electron releasing, neutral and electron withdrawing substituted derivatives are well tolerant and provides good yields of the corresponding phenoxazine derivatives.

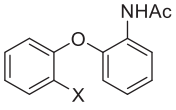
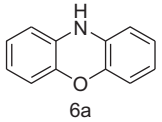
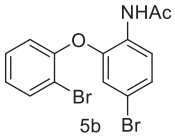
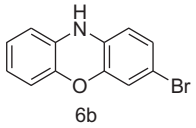
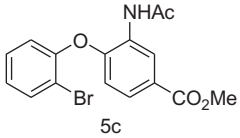
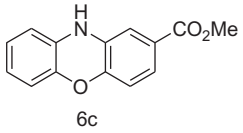
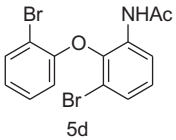
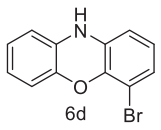
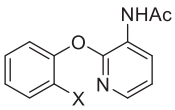
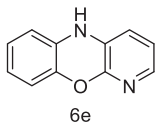
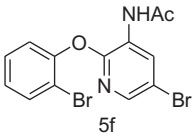
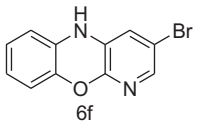
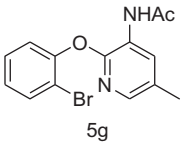
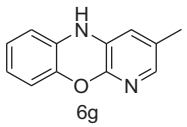
The substrates (**5a–5h**) synthesized from 2-halophenol (**1**) and substituted nitro derivatives (**2a–2h**) provided phenoxazines (**6a–6h**) in good yields as single isomer. To further support that the reaction proceeds through Smiles rearrangement, the substituted aryloxy acetanilides (**5i–5n**) synthesized from substituted phenols (**1i–1n**) were attempted for cyclization, resulting in the formation of rearranged products (**6i–6n**) in

Table 2. Synthesis of substituted phenoxazines/benzopyridoxazines.

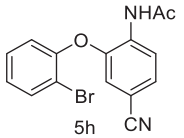
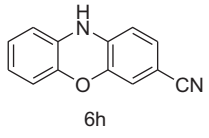
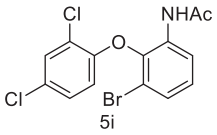
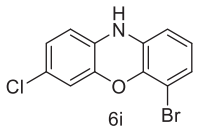
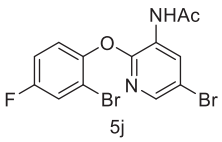
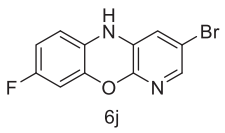
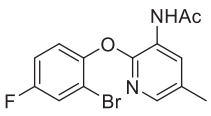
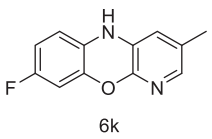
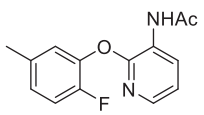
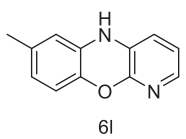
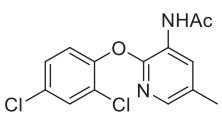
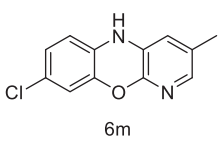
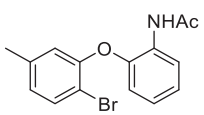
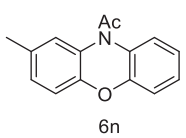


5a-n
X= I, Br, Cl, F
Y= C, N

6a-n

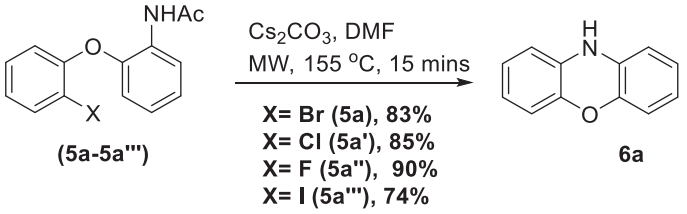
Entry	Substrate **5**	Product **6**	Yield (%)[a]
1		 6a	X = Br, 83 X = Cl, 85 X = F, 90 X = I, 74
2	 5b	 6b	82
3	 5c	 6c	88
4	 5d	 6d	76
5	 5e, 5e'	 6e	X= Br, 77 X= I, 80
6	 5f	 6f	73
7	 5g	 6g	72

(*continued*)

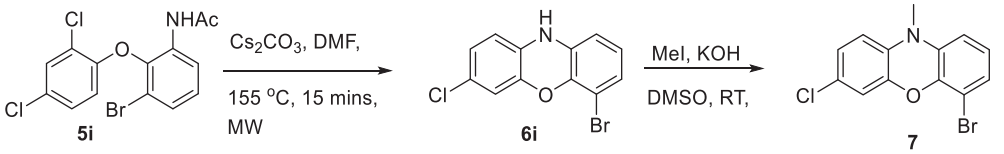
8	 5h	 6h	83
9	 5i	 6i	66
10	 5j	 6j	72
11	 5k	 6k	66
12	 5l	 6l	75
13	 5m	 6m	67
14	 5n	 6n	69[b]

Reaction conditions: (**5a–5n)** (0.5 mmol), Cs_2CO_3 (1.0 mmol), DMF (10 V) in MW for 15 min. [a]Yield of isolated products. [b]We obtained major acetyl phenoxazine (**6n**) over deacetylated product <10% (not isolated).

moderate yields. The isolated products were well characterized and verified by 2 D NMR data (see supporting information). Our attempts to get the single crystals for the isolated compounds were unsuccessful, as we noticed multi compounds in the same sample after crystallization. Probably, decomposed due to the solution phase instability or light sensitivity. In the case of example **6n,** we observed major *N*-acetyl phenoxazine (69%) over deacetylated product (<10%). Since the reaction condition is quite fast (15 min.), we could not isolate/detect a Smiles rearranged intermediate for the substrates (**5b–5n**). Also, the isolated phenoxazines were confirmed by 2 D NMR by correlating



Scheme 4. Generality of the cyclization with different leaving groups (**5a–5a**′′′).



Scheme 5. Synthesis of 6-bromo-3-chloro-10-methyl-10*H*-phenoxazine.

with exchangeable NH proton of phenoxazine, we alkylated one of the isolated phenoxazine 6-bromo-3-chloro-10*H*-phenoxazine **6i** to 6-bromo-3-chloro-10-methyl-10*H*-phenoxazine **7** (Scheme 5) and confirmed as well by methyl group interaction with arene protons of phenoxazine by 2 D NMR (see supporting information). With this conclusion, we report here that the cyclization reaction proceeds through Smiles/S_NAr cascade process.

Conclusion

We have described a general, highly chemo selective and metal free protocol for the construction of free NH-phenoxazines and benzopyridoxazines from *N*-acetyl diphenyl ethers. The optimized reaction condition worked well with the different leaving groups (F, Cl, Br, I) substituted *N*-acetyl diphenyl ethers affords the corresponding phenoxazines in moderate to good yields. As supported by trapping a Smiles intermediate (**5aa**) and structural confirmation of isolated phenoxazines (**6i–6n**) by 2 D NMR, we identified the reaction proceeds through Smiles rearrangement followed by intra molecular S_NAr cyclization. As the protocol involves metal free reaction condition, the substituted aryl halides (I, Br, Cl) were compatible and provides the free NH-phenoxazine and benzopyridoxazine scaffolds which we can used for further derivatization. Moreover, reaction requires a very short time and isolated yields are good to moderate irrespective of leaving groups and functional groups were attempted. Since the protocol involves microwave reactor, the high temperature reaction condition is a safe and convenient to adopt in laboratory scale synthesis.

Experimental section

General

Commercially available high purity grade chemicals were used as received without further purification. TLC was performed with aluminum sheets silica gel 60 F254 (Merck) and products were visualized by UV detection.^{1}H NMR and ^{13}C NMR spectra were

recorded on Bruker 300 or 400 MHz and 75 or 100 MHz spectrometer respectively in $CDCl_3/CD_3OD$/DMSO-d_6 using TMS as an internal standard. Chemical shifts (δ) are given in ppm relative to TMS. Coupling constants J are reported in Hz and coupling patterns are described as bs = broad singlet, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, td = triplet of doublet, q = quartet, m = multiplet. Mass spectra were recorded on Liquid Chromatography Mass Spectrometry (LCMS) or Ultra Performance Liquid Chromatography (UPLC). The compounds were isolated by Biotage Isolera silica gel flash chromatography using silica gel (40–63 µm, 60 Å). Microwave reactions were carried out using a Biotage Initiator 2.5 microwave synthesizer operating at 0–400 W irradiation power, at a normal absorption level. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

General experimental procedure for the synthesis of phenoxazines/benzopyridoxazines (6a–6n)

A microwave tube equipped with a magnetic stir bar was charged with the corresponding *N*-acetyl diphenyl ether (**5a–5n**) (1 mmol), Cs_2CO_3 (2 mmol) and DMF (20 V). The resultant reaction mixture was heated at 155 °C for 15 minutes by microwave irradiation. After completion of the reaction, water was added, extracted with ethyl acetate. The combined organic layer was dried over *anhydrous* Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by Biotage Isolera silica gel (40–63 µm, 60 Å) flash column chromatography (hexane/EtOAc, 95:5) to afford the corresponding phenoxazines/benzopyridoxazines (**6a–6n**).

Note: We noticed better recovery in the isolated yields, when the product was isolated and purified as soon as the reaction completed.

Synthesis of N-(2-bromophenyl)-N-(2-hydroxyphenyl)acetamide (5aa)

A microwave tube equipped with a magnetic stir bar was charged with *N*-(2-(2-bromophenoxy)phenyl)acetamide (**5a)** (0.10 g, 0.33 mmol), Cs_2CO_3 (0.107 g, 0.33 mmol) and DMF (20 V). The resultant reaction mixture was heated at 100 °C for 15 minutes by microwave irradiation. After completion of the reaction, water was added, extracted with ethyl acetate. The combined organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by Biotage Isolera silica gel (40–63 µm, 60 Å) flash column chromatography (hexane/EtOAc, 80:20) to afford *N*-(2-bromophenyl)-*N*-(2-hydroxyphenyl)acetamide **5aa** 0.078 g (78% yield) as a off white solid. LCMS (ES + APCI-MS) calcd. For $C_{14}H_{12}BrNO_2$: 305.01, found $(M+H)^+$ = 306.0; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.50 (bs, 1H), 7.70 (d, J = 7.60 Hz, 1H), 7.48–7.12 (m, 5H), 7.10–6.81 (m, 2H), 1.93 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.99, 150.90, 142.12, 134.25, 130.81, 130.26, 130.18, 129.19, 128.74, 125.69, 123.56, 121.07, 120.51, 23.66; Anal calc. for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58%; found C, 55.01; H, 2.85; N, 4.39%.

10h-phenoxazine (6a)

Following the general procedure using *N*-(2-(2-bromophenoxy)phenyl)acetamide **5a** (0.50 g, 1.63 mmol)) provided 0.25 g (83% yield) of the product **6a** as a white solid.

LCMS (ES + APCI). calcd. For $C_{12}H_9NO$: 183.06, found $(M+H)^+ =$ 184.0; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.16 (s, 1H), 6.71 (td, $J = 1.60$, 7.40 Hz, 2H), 6.60–6.53 (m, 4H), 6.44 (dd, $J = 1.20$, 7.60 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 143.23, 132.88, 124.37, 120.78, 115.52, 113.74. The analytical data are consistent with previous reports.[20].

Synthesis of 1-(10H-phenoxazin-10-yl)ethan-1-one (6aa)

A microwave tube equipped with a magnetic stir bar was charged with the *N*-(2-(2-bromophenoxy)phenyl)acetamide **5a** (0.155 g, 0.5 mmol), Na_2CO_3 (0.11 g, 1.0 mmol) and DMF (20 V). The resultant reaction mixture was heated at 130 °C for 30 minutes by microwave irradiation. After completion of the reaction, water was added, extracted with ethyl acetate. The combined organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by Biotage Isolera silica gel (40–63 µm, 60 Å) flash column chromatography (hexane/EtOAc, 95:5) to afford 8 mg (7% yield) of the product **6aa** as a white solid; LCMS (ES + APCI-MS) calcd. For $C_{14}H_{11}NO_2$: 225.08, found $(M+H)^+ =$ 226.2; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.62–7.60 (m, 2H), 7.28–7.16 (m, 6H), 2.27 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 169.27, 150.80, 129.69, 127.49, 125.88, 124.05, 117.07, 23.19. The analytical data are consistent with previous reports.[14]

Synthesis of 6-bromo-3-chloro-10-methyl-10H-phenoxazine (7)

To a stirred solution of 6-bromo-3-chloro-10*H*-phenoxazine (**6i**) (0.10 g, 0.34 mmol) in DMSO (10 V) was added KOH (0.64 mmol) at 0 °C. The resulting solution was stirred at RT for 15 mins. Then added MeI (0.37 mmol) in one lot. The reaction mixture was stirred at RT for 18 h. The reaction mixture was diluted with water, extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered through a cotton plug and concentrated under reduced pressure. The resulting crude was purified by Biotage Isolera silica gel (40–63 µm, 60 Å) flash column chromatography (hexane/EtOAc, 95:5) to afford 0.085 g (81% yield) of 6-bromo-3-chloro-10-methyl-10*H*-phenoxazine (**7**) as a off white solid. LCMS (ES + APCI-MS) calcd. For $C_{13}H_9BrClNO$: 308.9, found $(M+H)^+ =$ 310.9; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.91 (dd, $J = 1.20$, 8.20 Hz, 1H), 6.84 (d, $J = 2.40$, Hz, 1H), 6.83–6.82 (m, 1H), 6.72 (t, $J = 8.00$ Hz, 1H), 6.43 (dd, $J = 1.20$, 8.00 Hz, 1H), 6.41 (d, $J = 8.00$ Hz, 1H), 3.01 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 145.49, 142.10, 135.81, 133.23, 125.88, 124.85, 124.55, 123.88, 116.17, 112.06, 110.57, 109.48, 31.25; Anal calc. for $C_{13}H_9BrClNO$: C, 50.27; H, 2.92; N, 4.51%; found C, 50.01; H, 3.10; N, 4.68%.

Acknowledgments

The authors are thankful to Dr. Subhendu Kumar Mohanty, Dr. Sathya Shanker and Karthik T. Pai for their support and encouragement throughout this work. Kavitha is grateful to Syngene International Ltd, Bangalore, India for analytical support and the permission for higher education (Ph.D.).

Funding

, Kavitha is grateful to Syngene International Ltd, Bangalore, India for financial support.

References

[1] (a) Hendrich, A. B.; Stańczak, K.; Komorowska, M.; Motohashi, N.; Kawase, M.; Michalak, K. *Bioorg. Med. Chem.* **2006**, *14*, 5948–5954. DOI: 10.1016/j.bmc.2006.05.021. (b) Gao, S.; Takano, T.; Sada, K.; He, J.; Noda, C.; Hori-Tamura, N.; Tomoda, A.; Yamamura, H. B. *J. Pharmacol.* **2002**, *137*, 749–755.(c) Moosmann, B.; Skutella, T.; Beyer, K.; Behl, C. *Biol. Chem.* **2001**, *382*, 1601–1612. DOI: 10.1515/BC.2001.195.

[2] Thimmaiah, K. N.; Horton, J. K.; Seshadri, R.; Israel, M.; Houghton, J. A.; Harwood, F. C.; Houghton, P. J. *J. Med. Chem.* **1992**, *35*, 3358–3364. DOI: 10.1021/jm00096a009.

[3] McCarthy, B. G.; Pearson, R. M.; Lim, C.-H.; Sartor, S. M.; Damrauer, N. H.; Miyake, G. M. *J. Am. Chem. Soc.* **2018**, *140*, 5088–5101. DOI: 10.1021/jacs.7b12074.

[4] (a) Shelkovnikov, V. V.; Kolchina, E. F.; Gerasimova, T. N.; Eroshkin, V. I.; Zinin, E. I. *Nucl. Instrum. Methods* **1987**, *261*, 128–130. DOI: 10.1016/0168-9002(87)90579-1. (b) Dass, C.; Thimmaiah, K. N.; Jayashree, B. S.; Seshadri, R.; Israel, M.; Houghton, P. J. *Biol. Mass Spectrom.* **1994**, *23*, 140–146. DOI: 10.1002/bms.1200230304.

[5] (a) Tian, H.; Yang, X.; Cong, J.; Chen, R.; Liu, J.; Hao, Y.; Hagfeldt, A.; Sun, L. *Chem. Commun.* **2009**, *2009*, 6288–6290. (b) Karlsson, K. M.; Jiang, X.; Eriksson, S. K.; Gabrielsson, E.; Rensmo, H.; Hagfeldt, A.; Sun, L. *Chemistry* **2011**, *17*, 6415–6424. DOI: 10.1002/chem.201003730.

[6] Yang, X.-B.; Yang, B.-X.; Ge, J.-F.; Xu, Y.-J.; Xu, Q.-F.; Liang, J.; Lu, J.-M. *Org. Lett.* **2011**, *13*, 2710–2713. DOI: 10.1021/ol2008022.

[7] Jahanfar, M.; Suwa, K.; Tsuchiya, K.; Ogino, K. *OJOPM* **2013**, *03*, 46–52. DOI: 10.4236/ojopm.2013.32008.

[8] (a) Zhenqiang, J.; He, H.; Zhiqi, H.; Liao, S.; Peng, F.; Zhong, Z.; Guo, T.; Ying, L.; Cao, Y. *J. Mater. Chem. C* **2019**, *7*, 13859–13866. (b) Lee, C. W.; Kim, O. Y.; Lee, J. Y. *J. Ind. Eng. Chem.* **2014**, *20*, 1198–1208. DOI: 10.1016/j.jiec.2013.09.036.

[9] Farmer, L. A.; Haidasz, E. A.; Griesser, M.; Pratt, D. *J. Org. Chem.* **2017**, *82*, 10523–10536. DOI: 10.1021/acs.joc.7b02025.

[10] (a) Kolchina, E. F.; Gerasimova, T. N. *J. Fluor. Chem.* **1988**, *41*, 345–356. DOI: 10.1016/S0022-1139(00)81035-0. (b) Bonvicino, G. E.; Yogodzinski, L. H.; Jr.; Hardy, R. A. *J. Org. Chem.* **1961**, *26*, 2797–2803. DOI: 10.1021/jo01066a042.(c) Schmidt, D. M.; Bonvicino, G. E. *J. Org. Chem.* **1984**, *49*, 1664–1666. DOI: 10.1021/jo00183a039.(d) Orlov, V. D.; Kolos, N. N.; Rozhko, L. I.; Yaremenko, F. G.; Zolotarev, B. M.; Lavrushin, V. F. *Chem. Heterocycl. Compd.* **1981**, *17*, 544–548. DOI: 10.1007/BF00503476.

[11] (a) Wu, S.; Hu, W.-Y.; Zhang, S. L. *RSC Adv.* **2016**, *6*, 24257–24260. DOI: 10.1039/C6RA01295G. (b) Chowdhury, S. R.; Khdour, O. M.; Bandyopadhyay, I.; Hecht, S. M. *Bioorg. Med. Chem.* **2017**, *25*, 5537–5547. DOI: 10.1016/j.bmc.2017.08.021.

[12] Eastmond, G. C.; Gilchrist, T. L.; Paprotny, J.; Steiner, A. *New J. Chem.* **2001**, *25*, 385–390. DOI: 10.1039/b008503k.

[13] Zhang, L.; Huang, X.; Zhen, S.; Zhao, J.; Li, H.; Yuan, B.; Yang, G. *Org. Biomol. Chem.* **2017**, *15*, 6306–6309. DOI: 10.1039/c7ob01540b.

[14] Thome, I.; Bolm, C. *Org. Lett.* **2012**, *14*, 1892–1895. DOI: 10.1021/ol3005134.

[15] Haidasz, E. A.; Pratt, D. A. *Org. Lett.* **2017**, *19*, 1854–1857. DOI: 10.1021/acs.orglett.7b00615.

[16] Eregowda, G. B.; Kalpana, H. N.; Hegde, R.; Thimmaiah, K. N. *Indian J. Chem.* **2000**, *39B*, 243–259.

[17] Kervefors, G.; Becker, A.; Dey, C.; Olofsson, B. *Beilstein J. Org. Chem.* **2018**, *14*, 1491–1497. DOI: 10.3762/bjoc.14.126.

[18] (a) El Kaïm, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153–2171. DOI: 10.1016/j.tet.2008.12.002. (b) El Kaïm, L.; Grimaud, L. *Mol. Divers*. **2010**, *14*, 855–867. DOI: 10.1007/s11030-009-9175-3.(c) El Kaïm, L.; Grimaud, L. *Eur. J. Org. Chem.* **2014**, *2014*, 7749–7762. DOI: 10.1002/ejoc.201402783.(d) Ganguly, N. C.; Mondal, P.; Roy, S.; Mitra, P. *RSC Adv*. **2014**, *4*, 55640–55648. DOI: 10.1039/C4RA11128A.(e) Snape, T. J. *Chem. Soc. Rev*. **2008**, *37*, 2452–2458. 18 DOI: 10.1039/b808960d.(f) Xia, S.; Wang, L.-Y.; Zuo, H.; Li, Z. *COS* **2014**, *10*, 935–946. DOI: 10.2174/15701794113106660081.(g) Shruti Dwivedi, J.; Kishore, D.; Sain, H. *Synth. Commun.* **2018**, *48*, 1377–1402. DOI: 10.1080/00397911.2018.1448090.(h) Katsamakas, S.; Zografos, A. L.; Sarli, V. *Curr. Med. Chem*. **2016**, *23*, 2972–2999. DOI: 10.2174/0929867323666160510123023.(i) Nunewar, S. N.; Muthyala, B. B.; Dastari, S.; Tangellamudi, N. D. *New J. Chem.* **2019**, *43*, 14952–14960. DOI: 10.1039/C9NJ03525G.(j) Ezeokonkwo, M. A.; Iloka, K. C.; Okoro, U. C.; Onoabedje, E. A.; Ebere Ezema, B.; Ibeanu, F. N.; Ugwu, D. I.; Eze, F. U.; Uzoewulu, C. P. *Orient. J. Chem.* **2019**, *35*, 1320–1326. DOI: 10.13005/ojc/350410.

[19] (a) Sapegin, V.; Sakharov, V. N.; Kalandadze, L. S.; Smirnov, A. V.; Khristolyubova, T. A.; Plakhtinskii, V. V.; Ivashchenko, A. V. *Mendeleev Commun.* **2008**, *18*, 281–283. DOI: 10.1016/j.mencom.2008.09.019. (b) Reinaud, O.; Capdevielle, P.; Maumy, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, *1991*, 2129–2134.

[20] Zhao, Y.-Q.; Yin, Y.-Q.; Liu, J.; Wang, G.-H.; Huang, J.; Zhu, L.-J.; Wang, J.-H. *Acta Pharmacol. Sin.***2016**, *37*, 1237–1250. DOI: 10.1038/aps.2016.60.