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Metal-free formal synthesis of phenoxazine

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Abstract

A transition metal-free formal synthesis of phenoxazine is presented. The key step of the sequence is a high-yielding *O*-arylation of a phenol with an unsymmetrical diaryliodonium salt to provide an *ortho*-disubstituted diaryl ether. This species was cyclized to acetylphenoxazine in moderate yield. The overall yield in the three-step sequence is 72% based on recovered diaryl ether. An interesting, unusually stable iodine(III) intermediate in the *O*-arylation was observed by NMR and could be converted to the product upon longer reaction time.
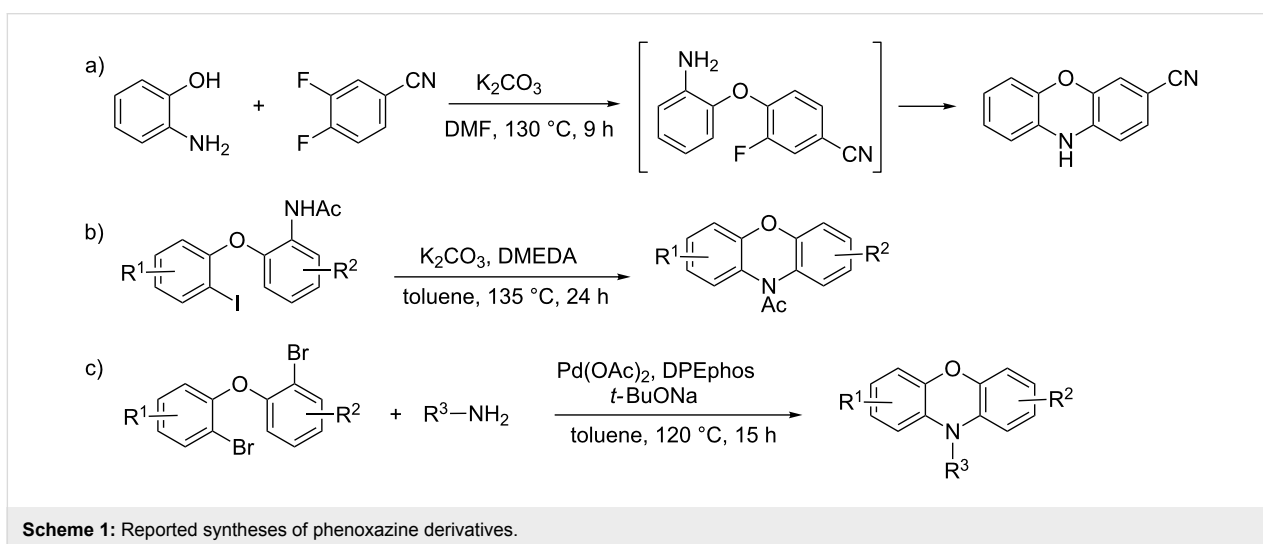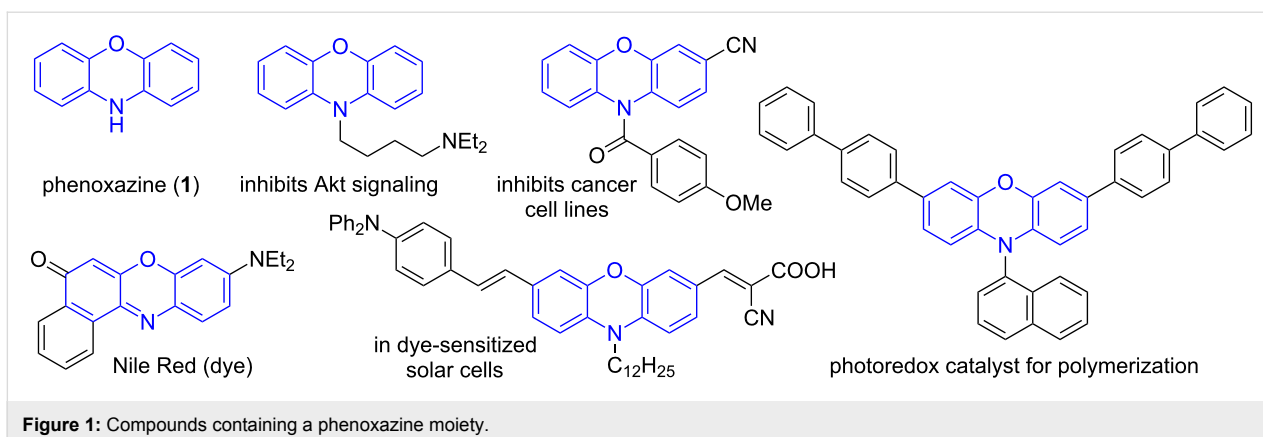
Introduction

Phenoxazine (**1**) is a tricyclic compound consisting of an oxazine ring fused between two benzene rings. A range of compounds with interesting biological or photophysical properties contain the phenoxazine core, where the amine moiety is either functionalized or oxidized to the corresponding imine [1-4]. Phenoxazine derivatives can display antitumor activity [5-8], are present in a variety of dyes [9], and can be applied in chemosensors and dye-sensitized solar cells (Figure 1) [10-12]. *N*-Arylphenoxazines were recently employed as photoredox catalysts in metal-free polymerizations [13].

The first synthesis of phenoxazine dates back more than 100 years [14], and a range of synthetic routes to this target has since been developed [1]. Transition metal-free routes include the synthesis from 2-aminophenols and 3,4-dihaloarenes deco-

rated with electron-withdrawing substituents, which proceed through a Smiles rearrangement (Scheme 1a) [15-17]. More recently, Bolm and co-workers reported a metal-free cyclization of iodo-substituted diaryl ethers with a broad scope (Scheme 1b) [18]. Transition metal-catalyzed cross couplings have also been employed to form the required C–O and C–N bonds, e.g., by Cu-catalyzed cyclization of 2-(2-bromophenoxy)anilines [17,19,20]. A Pd-catalyzed double *N*-arylation using di(2-bromoaryl) ethers and primary amines was recently developed (Scheme 1c) [21]. Furthermore, *N*-functionalization of the phenoxazine core can be performed under metal-free conditions [22].

Our research group has reported highly efficient *O*-arylations of phenols using diaryliodonium salts [23-25], which are reactive

Figure 1: Compounds containing a phenoxazine moiety.

Scheme 1: Reported syntheses of phenoxazine derivatives.

electrophilic arylation reagents [26-28]. As diaryliodonium salts can be easily synthesized in a one-pot manner [28], we envisioned that phenoxazines could be obtained in a straightforward and efficient manner from commercially available starting materials.

According to the retrosynthesis depicted in Scheme 2, target **1** would be formed from acetyl derivative **2**, which can be derived from the functionalized diaryl ether **3** using Bolm's *N*-arylation (see Scheme 1c) [18]. The synthesis of diaryl ether **3** is the key step of the sequence, proceeding via arylation of phenols with

Scheme 2: Retrosynthesis of phenoxazine.
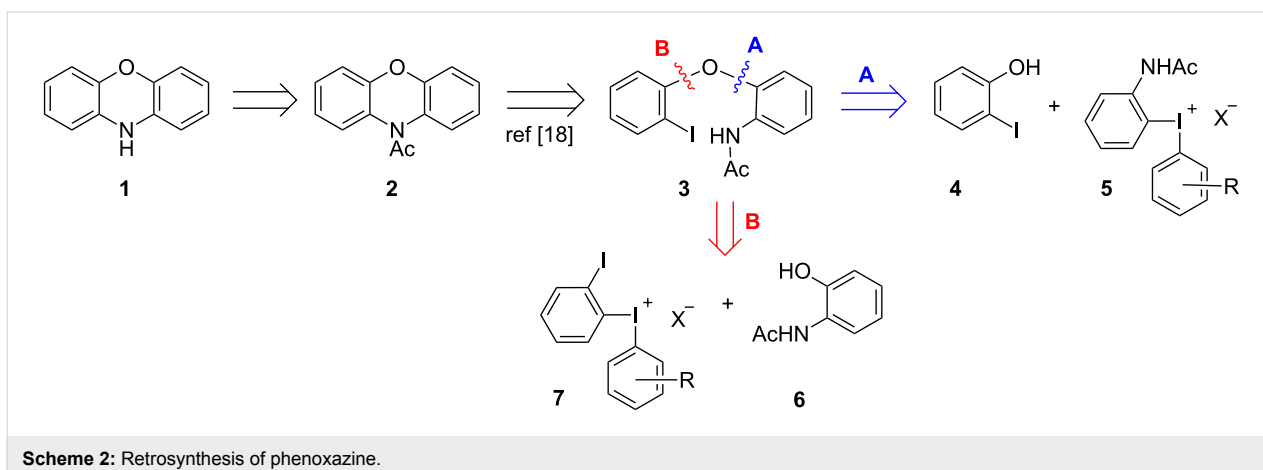
diaryliodonium salts using our reported methodology [23-25]. In reactions with unsymmetrical iodonium salts, this type of *O*-arylation is known to have an *ortho*-effect, i.e., chemoselective transfer of the *ortho*-substituted aryl moiety [29,30]. The use of unsymmetrical iodonium salts facilitates the synthesis of the reagents and avoids waste of an expensive iodoarene, and we hence envisioned chemoselective transfer of the desired aryl moiety from an unsymmetrical salt with a suitable "dummy" aryl group.

Two different approaches to reach **3** are illustrated, either employing 2-iodophenol (**4**) and 2-acetamido-substituted salt **5** (route A) or *N*-functionalized phenol **6** with 2-iodophenyl salt **7** (route B). In route A, the chemoselective transfer of the 2-amido aryl group over the other aryl group would require a quite electron-rich dummy group or the use of a symmetric iodonium salt (R = 2-NHAc). In route B, the challenge would instead be the synthesis of iodonium salt **7**, as the iodo substituent might be prone to oxidation. Furthermore, selective *O*-arylation in the presence of an amide moiety could be challenging, as *N*-arylation of amides with diaryliodonium salts proceeds at room temperature [31,32].

Results and Discussion

We initially focused on route A and decided to explore an anisyl moiety as dummy group in iodonium salt **5**. The electronic difference between the aryl groups in the formed salt should be sufficient to allow chemoselective transfer of the desired aryl moiety, and the *ortho*-effect exerted by the 2-amido substituent was expected to improve the chemoselectivity further. Salt **5a** was synthesized in good yield using our reported arylboronic acid methodology [33] (Scheme 3). Attempts to form the corresponding tosylate salt, either from iodoarene **8** with anisole and *m*CPBA/TsOH [34] or via anion exchange of **5a** were in vain.

The *O*-arylation of 2-iodophenol (**4**) with salt **5a** was investigated using our previously reported methodology [24,25]. As expected, the reaction proceeded well, both in THF and toluene, of which the latter was most appealing as it might allow a

tandem arylation and cyclization to reach *N*-acetylphenoxazine (**2**) in one pot. The arylations were analyzed by crude ^{1}H NMR yields using an internal standard and revealed that a minor amount of a byproduct was formed along with the expected diaryl ether **3** (Table 1, entry 1). This was initially believed to be 2-iodophenyl 4-anisyl ether, i.e., the diaryl ether that would form upon transfer of the anisyl moiety to the nucleophile. The reaction was thus further investigated to find conditions that would allow high yield of **3** with complete chemoselectivity.
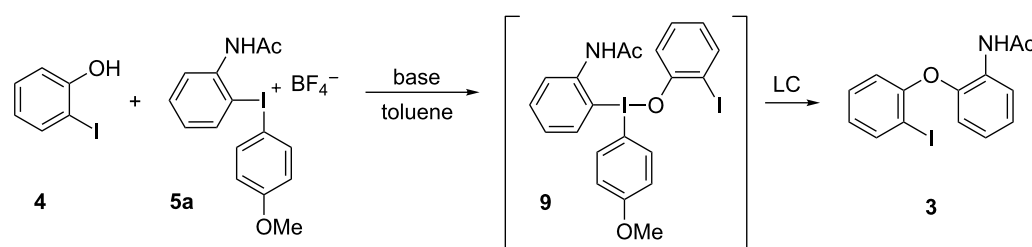
The amount of byproduct remained approximately constant when solvents and bases were screened (Table 1, entries 1–4, see also Supporting Information File 1), whereas certain changes in stoichiometry influenced the yield (Table 1, entries 5–7). Diaryl ether **3** was efficiently formed using the conditions in entry 7, and could be easily isolated by flash chromatography in 91% yield. A shortening of the reaction time to 1 h profoundly increased the amount of byproduct to 52% (Table 1, entry 8). Surprisingly, the desired product **3** could be isolated in 58% yield from this experiment after prolonged storage of the neat crude product at rt, along with 52% of 4-iodoanisol (see Supporting Information File 1).

This observation is in line with a ligand-coupling (LC) mechanism [30,35,36] where the observed byproduct could be the T-shaped intermediate **9** or the corresponding 4-coordinated species with two phenoxide units [37]. This type of intermediate is expected in LC reactions but can rarely be detected. The groups of Quideau and Muñiz have reported such compounds using an *ortho*-nitro substituted phenol and tetrafluorophthalimide as nucleophiles, respectively [38,39]. Those compounds were isolable at room temperature and could be converted to the arylated products upon heating. The reactivity of **9** is unusual, as it proved stable to neutral work-up with brine, formed product **3** upon longer reaction time or rt storage in CDCl$_3$ or neat, but decomposed to starting materials upon work-up with sat. ammonium chloride solution (Table 1, entry 11).

Due to the successful outcome of route A, pathway B was only briefly explored. Several dummy groups were considered for
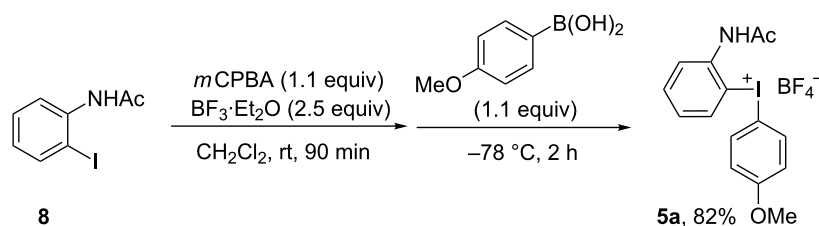
Scheme 3: Synthesis of iodonium salt **5a**.

Table 1: Optimization of the *O*-arylation of route A.[a]

| entry	phenol 4 (equiv)	salt 5a (equiv)	base (equiv)	T (°C)	time (h)	yield 3 (%)[b]	yield byproduct (%)[c]
1	1	1.1	*t*-BuOK (1.1)	rt	18	80	3
2[d]	1	1.1	*t*-BuOK (1.1)	rt	18	67	2
3	1	1.1	NaH (1.1)	rt	18	14	2
4	1	1.1	K₂CO₃ (1.1)	rt	18	65	2
5	1	1.5	*t*-BuOK (1.1)	rt	18	77	4
6	1	1.5	*t*-BuOK (1.5)	rt	18	74	14
7	**1.5**	**1**	***t*-BuOK (1.5)**	**rt**	**18**	**89 (91)**	**5**
8	1.5	1	*t*-BuOK (1.5)	rt	1	9 (58)	52
9	1	1	*t*-BuOK (1.5)	40	1	49	38
10	1.5	1	*t*-BuOK (1.5)	80	1	79	4
11[e]	1.5	1	*t*-BuOK (1.5)	rt	1	7	trace

[a]Phenol **4** (0.2 mmol) and base were stirred in anhydrous toluene (1 mL) for 30 min at rt before addition of **5a**. The reaction was stirred at the tabulated temperature and time and quenched with brine (see Supporting Information File 1 for details). [b]1H NMR yield using dibromomethane as internal standard (isolated yield in parenthesis). [c]1H NMR yield based on the assumption of one OMe group in byproduct, see Supporting Information File 1. [d]0.5 mL DME as co-solvent. [e]Quenched with sat. ammonium chloride solution instead of brine.

the iodonium salt **7**. A phenyl dummy might give sufficient chemoselectivity due to the *ortho*-effect, and the synthesis of salt **7a** was straightforward using 2-iodophenylboronic acid (Scheme 4a). The use of an anisyl dummy proved more difficult, and tetrafluoroborate **7b** was isolated with impurities using the arylboronic acid methodology [33] (Scheme 4b). The *m*CPBA/TsOH methodology [34] with 1,2-diiodobenzene (**10**) and anisole or trimethoxybenzene (TMP-H) as dummy surprisingly delivered the corresponding bisiodonium ditosylates [40-42] instead of the desired **7** (Scheme 4c, see also Supporting Information File 1). The stoichiometry of the reaction did not allow complete formation of **11**, but the yield based on TMP-H was 89%.

The arylation of phenol **6** with unsymmetrical diaryliodonium salt **7a** provided the desired diaryl ether **3** in modest yield and limited chemoselectivity (Scheme 5). Competitive *N*-arylation of the amide moiety [31,32] was not observed. Preliminary attempts to employ the bisiodonium salt **11** in the arylation of **6** were fruitless (see Supporting Information File 1), and we hence concluded that route A was most suitable for further investigations.

With high-yielding conditions for the *O*-arylation step at hand (Table 1, entry 7), the literature-reported [18] cyclization of **3** to *N*-acetylphenoxazine (**2**) was performed (Scheme 6a). In our hands, however, product **2** could only be isolated in 49% yield as the cyclization did not reach completion. The ratio of product **2** to starting material **3** remained 1:1 also upon modified conditions (see Supporting Information File 1). Still, the reaction was clean and the yield based on recovered starting material was 96%. The limited conversion into product **2** complicated our aim to perform the arylation and cyclization in one pot. The tandem reaction set up depicted in Scheme 6b delivered the *O*-arylated **3** in 87% yield, rather than product **2**, further illustrating the sensitivity of the cyclization step. Attempts to perform the cyclization with *t*-BuOK and DMEDA only resulted in byproduct formation.

The deprotection of **2** is reported to proceed in high yield [18], and the synthesis of **2** hence constitutes a metal-free formal synthesis of phenoxazine (**1**). The complete route is depicted in Scheme 7 and delivered *N*-acetylphenoxazine (**2**) in 72% overall yield over 3 steps. Combined with the literature yield for the deprotection, this would provide the target **1** in 65% overall
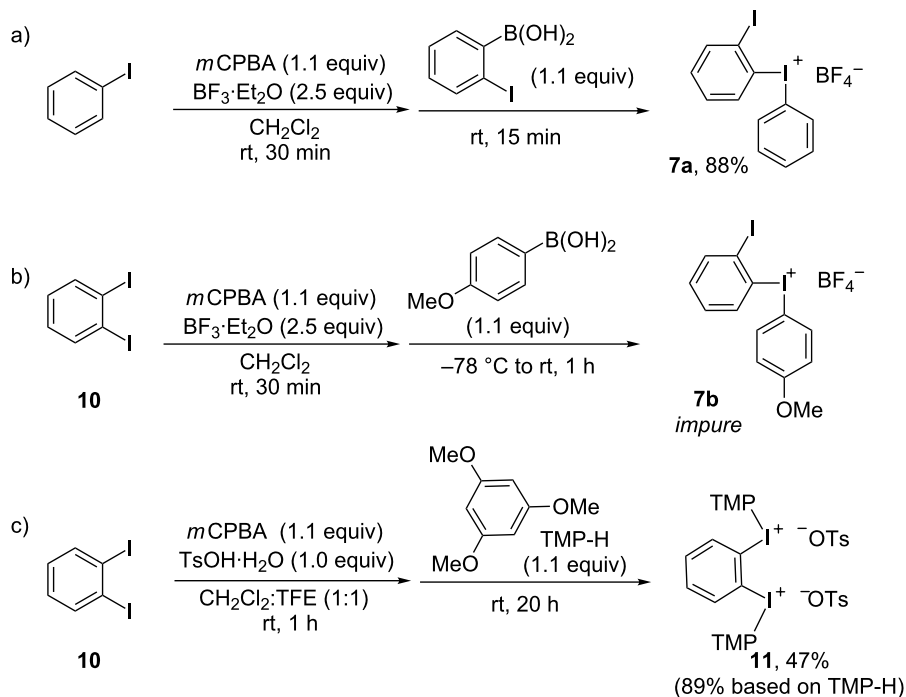
Scheme 4: Synthesis of iodonium salt **7**.
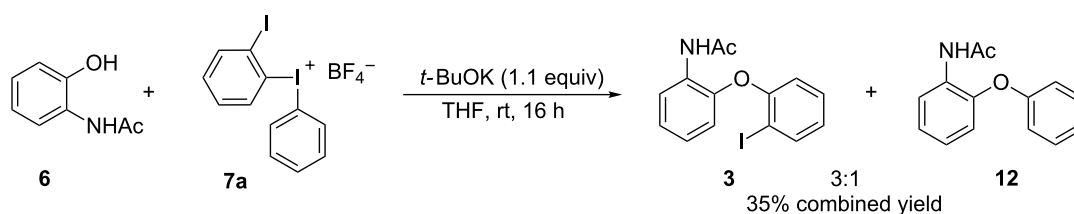
Scheme 5: *O*-Arylation via route B.
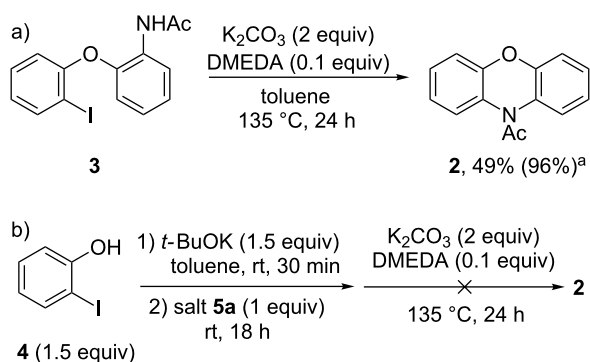
Scheme 6: a) Cyclization of diaryl ether **3**. b) Attempted one pot-synthesis of **2**. [a]Based on recovered **3**.

yield based on recovered **3**. The required starting materials in this route can easily be further substituted; hence we expect the methodology to be applicable also for phenoxazine derivatives.

Conclusion

A transition metal-free formal synthesis of phenoxazine is presented, relying on the *O*-arylation of phenol **4** with unsymmetrical diaryliodonium salt **5a** to provide substituted diaryl ether **3** as the key step. This species underwent an intramolecular *N*-arylation to provide the cyclized product **2**. The overall yield in this three-step sequence is 72% based on recovered diaryl ether. Interestingly, an unusually stable iodine(III) intermediate was formed in the *O*-arylation. This species survived neutral work-up and could be converted to product upon longer reaction time.

Scheme 7: Formal synthesis of phenoxazine (**1**). [a]Based on recovered **3**.
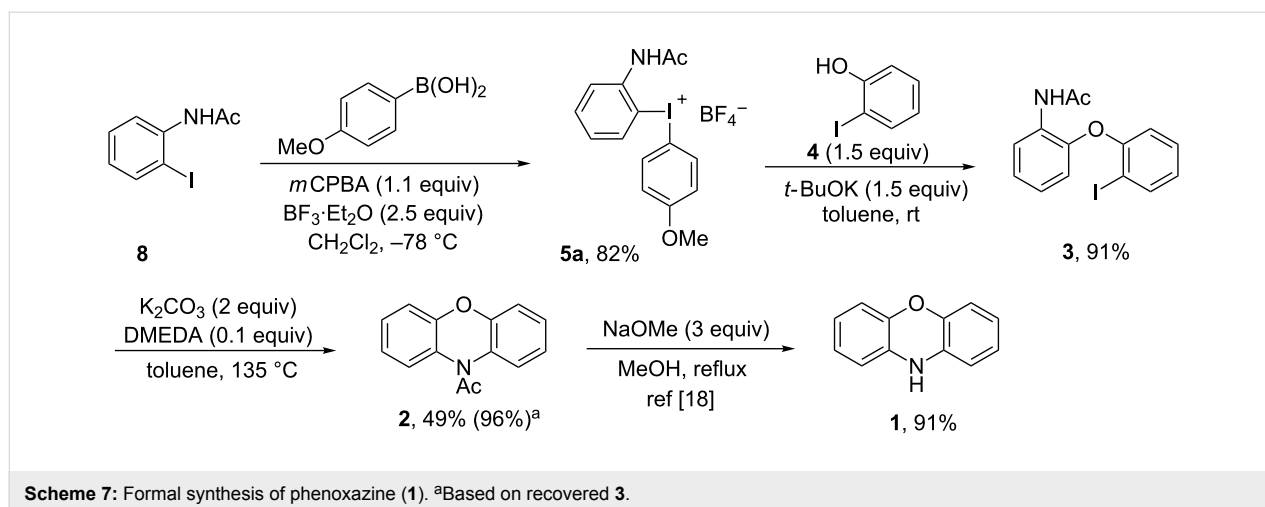
Supporting Information

Supporting Information File 1
Experimental details for the synthesis of starting materials and products, analytical data for products **2**, **3**, **5a**, **7a, 9** and **11**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-126-S1.pdf]

Supporting Information File 2
NMR spectra for products **2**, **3**, **5a**, **7a** and **11**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-126-S2.pdf]

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References
1. Katsamakas, S.; Zografos, A. L.; Sarli, V. *Curr. Med. Chem.* **2016,** *23,* 2972–2999. doi:10.2174/0929867323666160510123023
2. Hernandez-Olmos, V.; Abdelrahman, A.; El-Tayeb, A.; Freudendahl, D.; Weinhausen, S.; Müller, C. E. *J. Med. Chem.* **2012,** *55,* 9576–9588. doi:10.1021/jm300845v
3. Thimmaiah, K. N.; Easton, J. B.; Germain, G. S.; Morton, C. L.; Kamath, S.; Buolamwini, J. K.; Houghton, P. J. *J. Biol. Chem.* **2005,** *280,* 31924–31935. doi:10.1074/jbc.M507057200
4. Moosmann, B.; Skutella, T.; Beyer, K.; Behl, C. *Biol. Chem.* **2001,** *382,* 1601–1612. doi:10.1515/BC.2001.195
5. 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
6. Prinz, H.; Chamasmani, B.; Vogel, K.; Böhm, K. J.; Aicher, B.; Gerlach, M.; Günther, E. G.; Amon, P.; Ivanov, I.; Müller, K. *J. Med. Chem.* **2011,** *54,* 4247–4263. doi:10.1021/jm200436t
7. Avendaño, C.; Menéndez, J. C. *Medicinal Chemistry of Anticancer Drugs;* Elsevier: Amsterdam, 2008; pp 93–138. doi:10.1016/B978-0-444-52824-7.00004-4
8. Gao, S.; Takano, T.; Sada, K.; He, J.; Noda, C.; Hori-Tamura, N.; Tomoda, A.; Yamamura, H. *Br. J. Pharmacol.* **2002,** *137,* 749–755. doi:10.1038/sj.bjp.0704939
9. Martinez, V.; Henary, M. *Chem. – Eur. J.* **2016,** *22,* 13764–13782. doi:10.1002/chem.201601570
10. 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
11. Karlsson, K. M.; Jiang, X.; Eriksson, S. K.; Gabrielsson, E.; Rensmo, H.; Hagfeldt, A.; Sun, L. *Chem. – Eur. J.* **2011,** *17,* 6415–6424. doi:10.1002/chem.201003730
12. Tian, H.; Yang, X.; Cong, J.; Chen, R.; Liu, J.; Hao, Y.; Hagfeldt, A.; Sun, L. *Chem. Commun.* **2009,** 6288–6290. doi:10.1039/b912746a
13. Pearson, R. M.; Lim, C.-H.; McCarthy, B. G.; Musgrave, C. B.; Miyake, G. M. *J. Am. Chem. Soc.* **2016,** *138,* 11399–11407. doi:10.1021/jacs.6b08068
14. Bernthsen, A. *Ber. Dtsch. Chem. Ges.* **1887,** *20,* 942–944. doi:10.1002/cber.188702001214
15. Eastmond, G. C.; Gilchrist, T. L.; Paprotny, J.; Steiner, A. *New J. Chem.* **2001,** *25,* 385–390. doi:10.1039/b008503k
16. Schmidt, D. M.; Bonvicino, G. E. *J. Org. Chem.* **1984,** *49,* 1664–1666. doi:10.1021/jo00183a039
17. Bonvicino, G. E.; Yogodzinski, L. H.; Hardy, R. A., Jr. *J. Org. Chem.* **1961,** *26,* 2797–2803. doi:10.1021/jo01066a042
18. Thomé, I.; Bolm, C. *Org. Lett.* **2012,** *14,* 1892–1895. doi:10.1021/ol3005134
19. Liu, N.; Wang, B.; Chen, W.; Liu, C.; Wang, X.; Hu, Y. *RSC Adv.* **2014,** *4,* 51133–51139. doi:10.1039/C4RA09593F
20. Eregowda, G. B.; Kalpana, H. N.; Hegde, R.; Thimmaiah, K. N. *Indian J. Chem.* **2000,** *39B,* 243–259.
21. 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

22. Louillat-Habermeyer, M.-L.; Jin, R.; Patureau, F. W.
    Angew. Chem., Int. Ed. **2015,** *54,* 4102–4104.
    doi:10.1002/anie.201500089
23. Lindstedt, E.; Ghosh, R.; Olofsson, B. *Org. Lett.* **2013,** *15,* 6070–6073.
    doi:10.1021/ol402960f
24. Jalalian, N.; Petersen, T. B.; Olofsson, B. *Chem. – Eur. J.* **2012,** *18,*
    14140–14149. doi:10.1002/chem.201201645
25. Jalalian, N.; Ishikawa, E. E.; Silva, L. F., Jr.; Olofsson, B. *Org. Lett.*
    2011, *13,* 1552–1555. doi:10.1021/ol200265t
26. Aradi, K.; Tóth, B. L.; Tolnai, G. L.; Novák, Z. *Synlett* **2016,** *27,*
    1456–1485. doi:10.1055/s-0035-1561369
27. Olofsson, B. *Top. Curr. Chem.* **2016,** *373,* 135–166.
    doi:10.1007/128_2015_661
28. Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009,** *48,*
    9052–9070. doi:10.1002/anie.200904689
29. Stuart, D. R. *Chem. – Eur. J.* **2017,** *23,* 15852–15863.
    doi:10.1002/chem.201702732
30. Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B.
    Chem. – Eur. J. **2013,** *19,* 10334–10342. doi:10.1002/chem.201300860
31. Tinnis, F.; Stridfeldt, E.; Lundberg, H.; Adolfsson, H.; Olofsson, B.
    Org. Lett. **2015,** *17,* 2688–2691. doi:10.1021/acs.orglett.5b01079
32. Wang, M.; Huang, Z. *Org. Biomol. Chem.* **2016,** *14,* 10185–10188.
    doi:10.1039/C6OB01649A
33. Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008,** *73,*
    4602–4607. doi:10.1021/jo8004974
34. Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008,** 592–596.
    doi:10.1055/s-2008-1032050
35. Ochiai, M. *Top. Curr. Chem.* **2003,** *224,* 5–68.
    doi:10.1007/3-540-46114-0_2
36. Pinto de Magalhães, H.; Lüthi, H. P.; Togni, A. *Org. Lett.* **2012,** *14,*
    3830–3833. doi:10.1021/ol3014039
37. Stridfeldt, E.; Lindstedt, E.; Reitti, M.; Blid, J.; Norrby, P.-O.;
    Olofsson, B. *Chem. – Eur. J.* **2017,** *23,* 13249–13258.
    doi:10.1002/chem.201703057
38. Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005,** *44,*
    7065–7069. doi:10.1002/anie.200501638
39. Lucchetti, N.; Scalone, M.; Fantasia, S.; Muñiz, K.
    Angew. Chem., Int. Ed. **2016,** *55,* 13335–13339.
    doi:10.1002/anie.201606599
40. Dohi, T.; Kato, D.; Hyodo, R.; Yamashita, D.; Shiro, M.; Kita, Y.
    Angew. Chem., Int. Ed. **2011,** *50,* 3784–3787.
    doi:10.1002/anie.201007640
41. Stang, P. J.; Zhdankin, V. V. *J. Am. Chem. Soc.* **1993,** *115,*
    9808–9809. doi:10.1021/ja00074a061
42. Kitamura, T.; Furuki, R.; Nagata, K.; Taniguchi, H.; Stang, P. J.
    J. Org. Chem. **1992,** *57,* 6810–6814. doi:10.1021/jo00051a025