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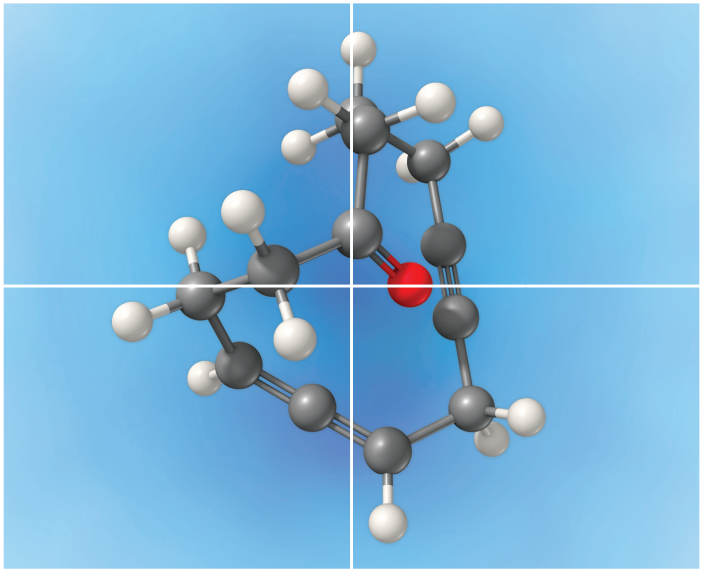

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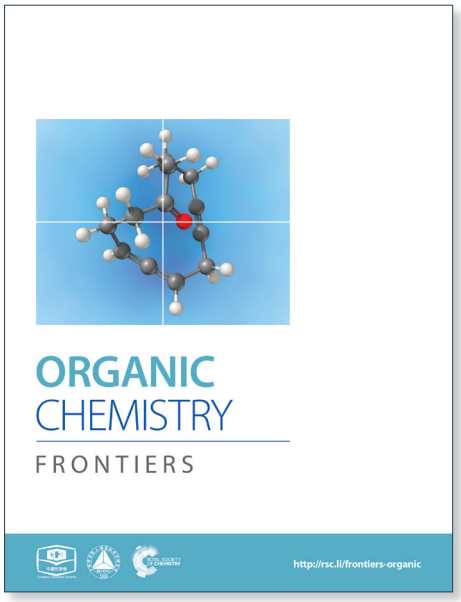

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ARTICLE TYPE

Imino Exchange Reaction in Dearomatization Strategy: Synthesis of *N*-Acyl Diarylamines and Phenothiazines from Two Anilines

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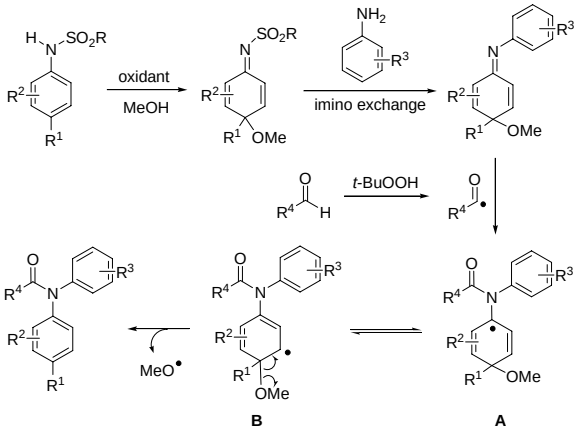
***N*-Sulfonyl cyclohexadienimines generated from an iodine(III)-induced oxidative dearomatization of *N*-sulfonyl protected *para*-substituted anilines are ready to undergo an imino exchange reaction with another aniline, which provides an alternative way to access *N*-acyl diarylamines and phenothiazines.**

As a result of the inherent reactivity stored within the aromatic systems, dearomatization strategy has been intensively explored and utilized as a powerful tool in organic synthesis.[1] The oxidative dearomatization of *para*-substituted anilines forms cyclohexadienimines, and these dearomatized products have proved to be highly reactive intermediates for various 1,4-additions.[2,3] However, some of our recent studies revealed that a 1,2-imino exchange reaction of *N*-sulfonyl cyclohexadienimines might be preferred over the 1,4-addition when another aniline was used as nucleophile. This reaction offers strategic opportunities for preparing a variety of diarylamine derivatives[4] from two anilines. Herein, we wish to present our success in applying this strategy in the synthesis of *N*-acyl diarylamines and phenothiazines.

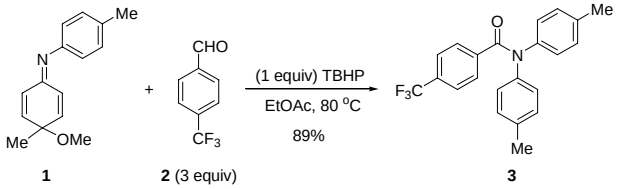
We conceived that the aromatization of the imino exchanged product (*N*-aryl cyclohexadienimine) might perform via a single-electron-transfer way triggered by a free radical. As shown in Scheme 1, the addition of an *in situ* generated aldehydic radical[5] to the nitrogen-carbon double bond of *N*-aryl cyclohexadienimine affords a radical intermediate **A**.[6] After an isomerisation and a *β*-scission, *N*-acyl diarylamine is formed.

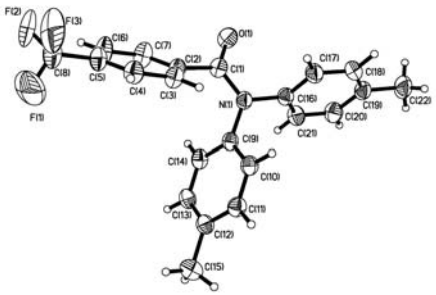
We initiated our investigation on the reaction of *N*-aryl cyclohexadienimine **1** with 4-(trifluoromethyl)benzaldehyde **2** and TBHP. Among the reaction solvents and temperatures examined, ethyl acetate proved to be the best reaction media at 80 ºC. The best ratio of *N*-aryl cyclohexadienimine, 4-methoxybenzaldehyde, and TBHP was 1:3:1, leading to *N*-acyl diarylamine **3** in 89% yield. The structure of compound **3** was confirmed by its single-crystal diffraction analysis (Scheme 2).[7]

With the optimized reaction conditions established, the synthesis of *N*-acyl diarylamines from anilines and aldehydes was investigated (Table 1). The $PhI(OAc)_2$-induced oxidative dearomatization and the $Bi(OTf)_3$-catalyzed 1,2-imino exchange reaction were conducted in methanol in one pot. After a simple workup process, the crude mixture was treated with aldehydes and TBHP. For most cases, the reaction proceeded smoothly and afforded *N*-acyl diarylamines in moderate to good yields. With



Scheme 1 Synthesis of *N*-acyl diarylamines using dearomatization strategy



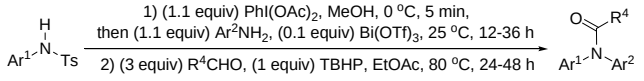


Scheme 2 Formation of *N*-acyl diarylamine **3** and its X-ray diffraction structure

respect to aldehydes, arylaldehydes bearing a range of substituents were suitable reaction partners. The reaction of butyraldehyde did not give rise to the desired product. A variety of anilines were suitable substrates for this three-step synthesis. The imino exchange reaction with 4-amino-pyridine was complex.

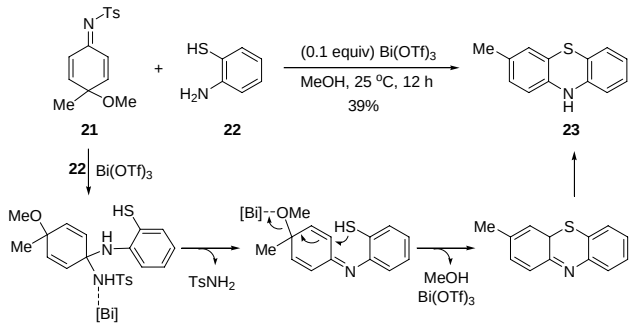
Interestingly, under the standard conditions, an unexpected product, phenothiazine **23**, was isolated in 39% yield from the

Table 1 Synthesis of *N*-acyl diarylamines from anilines and aldehydes



Entry	Ar^1	Ar^2	R^4	Product (%)[a]
1	4-MeC_6H_4	4-MeC_6H_4	4-$CF_3C_6H_4$	**3** (82)
2	4-MeC_6H_4	4-MeC_6H_4	4-FC_6H_4	**4** (80)
3	4-MeC_6H_4	4-MeC_6H_4	4-CNC_6H_4	**5** (83)
4	4-MeC_6H_4	4-MeC_6H_4	4-$NO_2C_6H_4$	**6** (82)
5	4-MeC_6H_4	4-MeC_6H_4	4-ClC_6H_4	**7** (86)
6	4-MeC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$	**8** (79)
7	4-MeC_6H_4	4-MeC_6H_4	C_6H_5	**9** (85)
8	4-MeC_6H_4	4-MeC_6H_4	*n*Pr	**10** (0)
9	4-EtC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$	**11** (75)
10	4-*n*-BuC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$	**12** (80)
11	4-*i*-PrC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$	**13** (76)
12	4-MeC_6H_4	C_6H_5	4-$MeOC_6H_4$	**14** (66)
13	4-MeC_6H_4	3,5-$(Me)_2C_6H_3$	4-$MeOC_6H_4$	**15** (62)
14	4-MeC_6H_4	3,4-$(Me)_2C_6H_3$	4-$MeOC_6H_4$	**16** (77)
15	4-MeC_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**17** (81)
16	4-MeC_6H_4	4-ClC_6H_4	4-$MeOC_6H_4$	**18** (85)
17	4-MeC_6H_4	4-FC_6H_4	4-$MeOC_6H_4$	**19** (76)
18	4-MeC_6H_4	4-pyridyl	4-$MeOC_6H_4$	**20** (0)

[a]Reported yields are of the isolated products.

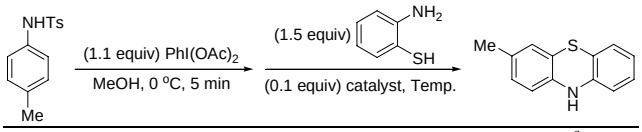


Scheme 3 Formation of phenothiazine **23**

imino exchange reaction with 2-aminobenzenethiol. It is proposed that this product was formed from an intramolecular trapping of the imino exchange intermediate by the thiol group (Scheme 3). Phenothiazines constitute a valuable class of compounds.[8] They are widely used as analgesic,[9] antiinflammatory,[10] antiplatelet,[11] and multiple drug resistance reverting agents.[12] Because of the importance of these compounds, recently, the groups of Jørgensen,[13] Ma,[14] and Zeng[15] have developed transition-metal catalyzed coupling reactions to prepare phenothiazines from a variety of aryl halides.

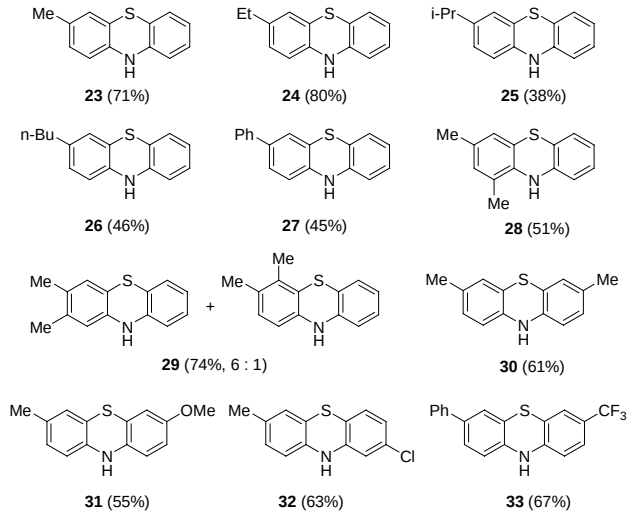
To develop an alternative way to access phenothiazines from anilines, various metal salts were examined to promote the formation of phenothiazine **23** in a one-pot reaction (Table 2). Copper(I) iodide proved to be the best Lewis acid to promote the imino exchange and the intramolecular trapping reaction. In the presence of 0.1 equiv of copper(I) iodide, the reaction at reflux gave rise to phenothiazines **23** in 71% yield (Table 2, entry 15). In the absence of the added catalysts, the one-pot reaction still produced compound **23** in 37% yield. But the formation of compound **23** was not observed when *N*-Ts cyclohexadienimine **21** was used in the absence of a catalyst. It is supposed that the formation of phenothiazine might also be promoted by acetic acid metabolized from $PhI(OAc)_2$ in dearomatization reaction. Under

Table 2 Evaluation of conditions for the formation of phenothiazine

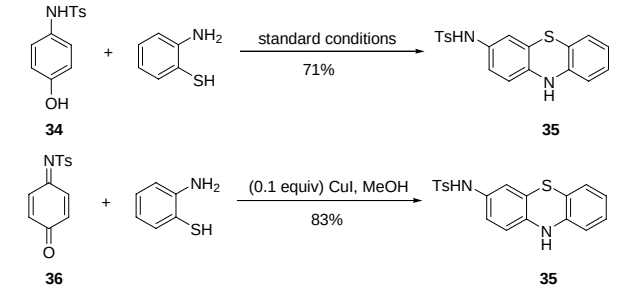


Entry	Catalyst	Temperature (°C)	**23**[a] (%)
1	$Bi(OTf)_3$ (0.1 equiv)	0–25	37
2	$Pd(OAc)_2$ (0.1 equiv)	0–25	28
3	AgOTf (0.1 equiv)	0–25	26
4	$Sc(OTf)_3$ (0.1 equiv)	0–25	27
5	$FeCl_3$ (0.1 equiv)	0–25	25
6	$Yb(OTf)_3$ (0.1 equiv)	0–25	25
7	$Zn(OTf)_2$ (0.1 equiv)	0–25	34
8	$Cu(OTf)_2$ (0.1 equiv)	0–25	43
9	$Cu(OAc)_2$ (0.1 equiv)	0–25	33
10	$CuCl_2$ (0.1 equiv)	0–25	36
11	$CuBr_2$ (0.1 equiv)	0–25	37
12	CuCl (0.1 equiv)	0–25	41
13	CuBr (0.1 equiv)	0–25	42
14	CuI (0.1 equiv)	0–25	48
15	CuI (0.1 equiv)	0–65	71
16	CuI (0.05 equiv)	0–65	57
17	CuI (0.2 equiv)	0–65	67

[a]Reported yields are of the isolated product.



Scheme 4 Synthesis of phenothiazines from 2-aminobenzenethiols and anilines



Scheme 5 Formation of phenothiazin-3-amine

the optimized conditions, a range of *para*-substituted anilines reacted with 2-aminobenzenethiols to afford the corresponding

phenothiazines in moderate to good yields (Scheme 4). When 3,4-dimethylbenzenamine was used, the attack by the thiol group at the less hindered position was preferred.

It is noteworthy that when *N*-Ts protected 4-aminophenol **34** was used as substrate, the reaction afforded phenothiazin-3-amine **35** as product. *N*-Tosyl quinine monosulfonimide **36** isolated from the corresponding oxidative dearomatization reaction could be converted to compound **35** (Scheme 5).

In conclusion, we have developed an alternative method to prepare *N*-acyl diarylamines and phenothiazines from anilines using a dearomatization strategy. The key step in this strategy is the imino exchange reaction. Work is currently ongoing to explore its reaction mechanism and possible synthetic applications, and these results will be reported in due course.

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR of new compounds]. See DOI: 10.1039/b000000x/

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