The acid-promoted reactions of phenyliodonium ylides with substituted anilines and their applications to the synthesis of indoles†‡

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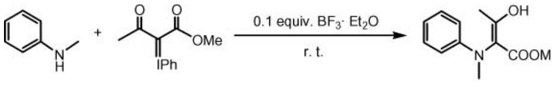
The *N*-substituted anilines 1 react readily with phenyliodonium ylides 2 derived from 1,3-dicarbonyl compounds in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$, forming the C–N coupling products 3, which are precursors for the synthesis of indoles. On the basis of this result, the direct synthesis of indoles from 1 and 2 under thermal conditions and photochemical conditions was explored. The transformations could be achieved in a one-pot way under thermal conditions or in a tandem manner under photochemical conditions.

Phenyliodonium ylides derived from 1,3-dicarbonyl compounds are useful synthetic intermediates.[1] The reactions between phenyliodonium ylides and transitional metals such as copper(I) and Rh(II) constitute a convenient approach to the corresponding carbenoids, which subsequently undertake C–H insertion or addition to alkenes.[2] In contrast to this well-known use of phenyliodonium ylides, their synthetic potential under metal-free conditions is far less explored.[3] We found recently that Lewis acids such as $BF_3{\cdot}Et_2O$ could catalyze the reactions between phenyliodonium ylides and electron-rich enamine esters, and the reactions could be used to prepare polysubstituted pyrrole products.[4] Further studies demonstrated that anilines could also react with phenyliodonium ylides in the presence of $BF_3{\cdot}Et_2O$. Based on this result and the literature work, the one-pot synthesis of indoles from anilines and phenyliodonium ylides was explored. Here we wish to report the results.

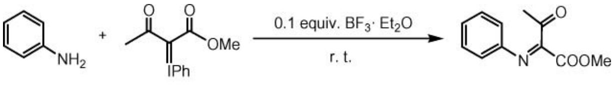


1a **2a** **3aa**

Solvent	Yield
CH_2Cl_2	73 %
$ClCH_2CH_2Cl$	40 %
CH_3OH	98 %
toluene	81 %
CH_3CN	71 %

(1)

The reaction was firstly investigated by applying the previously reported[4] reaction conditions to *N*-methyl aniline. Using 0.1 equiv. of $BF_3{\cdot}Et_2O$ as catalyst, *N*-methyl aniline **1a** readily reacted with phenyliodonium ylide **2a**, giving rise to the C–N coupling product **3aa** (eqn (1)). The reaction could be carried out in various solvents, but the best result was obtained when CH_3OH was used, in which the reaction finished in 5 min., and **3aa** was produced in excellent yield. By comparison, only a trace amount of products was generated in the absence of $BF_3{\cdot}Et_2O$. The *N*-unsubstituted aniline, on the other hand, reacted with **2a** to generate the imine product (eqn (2)).



2a

(2)

Following the brief screening of the reaction conditions, the scope of the reaction was then examined. As shown in Table 1, a variety of substituted anilines **1** reacted with phenyliodonium ylide **2** to generate **3**. The yields varied depending on the substituents in both **1** and **2**. While the yields were generally good for substrates **1a–1f**, and **1i**, the reactions with alkoxy group-substituted anilines gave the products in lower yields. (Table 1, entries 16–19). The reason for this might be that oxidation of the electron-rich anilines by phenyliodonium ylides led to decomposed products. On the other hand, *p*-NO_2-substituted *N*-methyl aniline was not reactive to **2** under the reaction conditions.

Compounds **3** are useful synthetic intermediates as they could be transformed to substituted indoles by way of the modified

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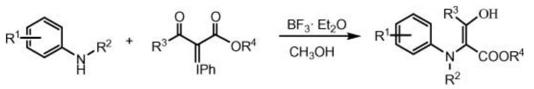
‡ **General procedure for the reactions of 1 with 2**: 13 μL of $BF_3{\cdot}Et_2O$ was added to the mixture of 1 mmol **1** and 1 mmol **2** in 2 mL methanol, and the mixture was stirred at room temperature for 5 min. The solvent was then removed under reduced pressure, and the residual was treated with silica gel chromatography to give the pure product **3**. **General procedure for the one-pot synthesis of indoles under thermal conditions**: A mixture of 1 mmol **1**, 1 mmol **2**, and 13 μL of $BF_3{\cdot}Et_2O$ in 3 mL toluene was stirred in a 10 mL round bottom flask at room temperature for 30 min. Then 300 mg of Amberlyst^{R} 15 was added into the reaction mixture, followed by fitting the flask with a condenser. The reaction mixture was then stirred at reflux for 12 h. The solvent was removed under reduced pressure, and the residual was subject to silica gel chromatography to give the indole product.[5c] **General procedure for the synthesis of indoles from 1 and 2 under photochemical conditions**: To a Pyrex tube containing a solution of 1 mmol **1** in 10 mL of benzene and 10 mL of methanol was added 1 mmol **2**. The solution was bubbled with argon for 15 min. Then 0.6 mL TFAA was added in and the solution was irradiated with a 500 W medium-pressure mercury lamp under argon atmosphere at room temperature for 12 h. After irradiation, the solvent was removed under reduced pressure, and the residual was treated with silica gel chromatography to give the product.

Table 1 $BF_3·Et_2O$-catalyzed coupling reactions of anilines (**1**) and phenyliodonium ylides (**2**)[a]

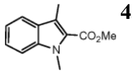
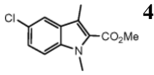
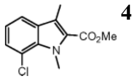
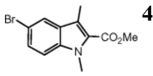
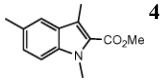
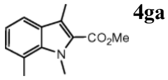
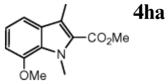
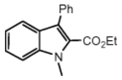
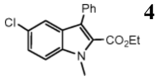
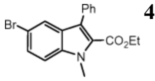


1 **2** **3**

		Substrates					
Entry	**1**	R^1	R^2	**2**	R^3	R^4	Product/Yield (%)[b]
1	**1a**	H	Me	**2a**	Me	Me	**3aa**/98
2	**1a**			**2b**	Ph	Et	**3ab**/93
3	**1a**			**2c**	Pr	Et	**3ac**/84
4	**1b**	*p*-Cl	Me	**2a**			**3ba**/89
5	**1b**			**2b**			**3bb**/63
6	**1c**	*o*-Cl	Me	**2a**			**3ca**/98
7	**1c**			**2b**			**3cb**/87
8	**1d**	*m*-Cl	Me	**2a**			**3da**/97
9	**1d**			**2b**			**3db**/90
10	**1e**	*p*-Br	Me	**2a**			**3ea**/91
11	**1e**			**2b**			**3eb**/55
12	**1e**			**2c**			**3ec**/89
13	**1f**	*p*-Me	Me	**2a**			**3fa**/97
14	**1f**			**2b**			**3fb**/72
15	**1f**			**2c**			**3fc**/73
16	**1g**	*p*-OEt	Me	**2a**			**3ga**/38
17	**1g**			**2b**			**3gb**/38
18	**1h**	*o*-OMe	Me	**2a**			**3ha**/47
19	**1h**			**2b**			**3hb**/56
20	**1i**	H	Bn	**2a**			**3ia**/94

[a] The reaction was carried out by stirring 1 mmol of **1**, 1 mmol of **2** and 13 μL of $BF_3·Et_2O$ in 2 mL CH_3OH for 5 min. [b] Isolated yields.

Table 2 One-pot synthesis of indoles from **1** and **2**

Entry	Substrates		Product	Yield (%)[a]
1	**1a**	**2a**	 **4aa**	52
2	**1b**	**2a**	 **4ba**	64
3	**1c**	**2a**	 **4ca**	14
4	**1e**	**2a**	 **4ea**	75
5	**1f**	**2a**	 **4fa**	61
6	**1g**	**2a**	 **4ga**	19
7	**1h**	**2a**	 **4ha**	14
8	**1a**	**2b**	 **4ab**	52
9	**1b**	**2b**	 **4bb**	18
10	**1e**	**2b**	 **4eb**	29

[a] Isolated yields.

Bischler indole synthesis[5] or under photochemical conditions.[6] **3** can be prepared through the reactions of anilines with the corresponding 2-halo-substituted *β*-keto esters[7] or with the metal carbenes derived from diazocarbonyl compounds.[5] The reactions of phenyliodonium ylides with substituted anilines thus provide an alternative approach to gain access to compounds **3**. As phenyliodonium ylides can be easily prepared from 1,3-dicarbonyl compounds and $PhI(OAc)_2$,[8] and only a catalytic amount of $BF_3·Et_2O$ was required, this method is advantageous in terms of simplicity and mildness.

The one-pot syntheses of substituted indoles from anilines and phenyliodonium ylides were explored next. It was demonstrated that the transformations from **3** to indoles proceeded most effectively in toluene at reflux with Amberlyst^R 15 as catalyst.[5] Therefore, the reactions were carried out in toluene firstly at room temperature with $BF_3·Et_2O$ as catalyst to generate **3**. Then Amberlyst^R 15 was added to the reaction mixture and the temperature was raised to allow refluxing of the solvent. The results are summarized in Table 2. As shown in Table 2, Indoles **4** were formed in reasonable yields for the reactions of *para*-substituted anilines with **2a**, whereas in the case of *ortho*-substituted anilines, the yields were low (Table 2, entries 3, 6 and 7). The yields were also unsatisfactory when **2b** was used as the substrate (entries 9 and 10).

The conversion of compounds **3** to the corresponding indoles **4** was reported to be highly efficient under photochemical conditions.[6] As such, the pyrex-filtered irradiation of **3** in an argon-purged benzene–methanol-acetic acid solution (15 : 15 : 1) effectively led to the formation of the corresponding indoles (Fig. 1). As the reaction medium was acidic, we envisioned that the indoles might be formed from **1** and **2** in a tandem manner. After some exploration of reaction conditions, we found that when trifluoroacetic acid anhydride (TFAA) was used as the source of the acid instead of acetic acid, the one-pot synthesis of indoles could be realized. The reaction was performed by irradiating an argon-purged Pyrex tube containing a solution of **1** and **2** in benzene–methanol-TFAA (10 : 10 : 0.6) with a medium-pressure mercury lamp, and the indole products formed in varied yields (Table 3). The yields of indoles **4bb** and **4eb** were higher than

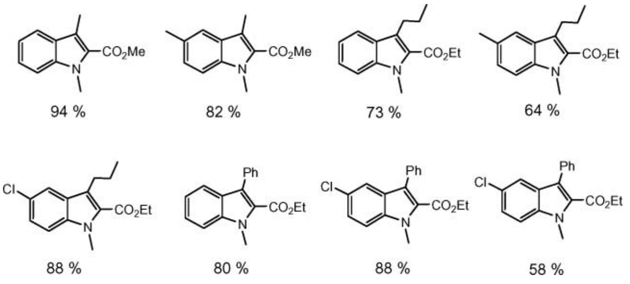
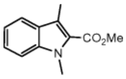
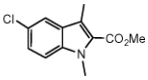
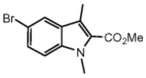
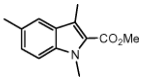
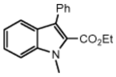
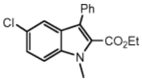
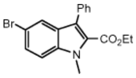
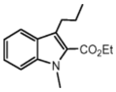
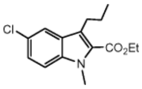
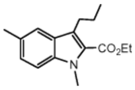


Fig. 1 Photosynthesis of indoles from **3**.

Table 3 The synthesis of indoles from **1** and **2** under photochemical conditions[a]

Entry	Substrates		Product	Yield (%)[b]
1	**1a**	**2a**	 **4aa**	52
2	**1b**	**2a**	 **4ba**	63
3	**1e**	**2a**	 **4ea**	46
4	**1f**	**2a**	 **4fa**	53
5	**1a**	**2b**	 **4ab**	41
6	**1b**	**2b**	 **4bb**	56
7	**1e**	**2b**	 **4eb**	36
8	**1a**	**2c**	 **4ac**	52
9	**1b**	**2c**	 **4bc**	36
10	**1f**	**2c**	 **4fc**	35

[a] To a Pyrex tube containing a mixture of 1 mmol **1** and **2** in 10 mL of benzene and 10 mL of methanol was added 0.6 mL TFAA. The solution was irradiated with a 500 W medium-pressure mercury lamp under argon atmosphere at room temperature for 12 h. [b] Isolated yields.

those shown in Table 2, while **4ea** and **4fa** were obtained in lower yields under photochemical conditions. In general, the results were comparable to those obtained by using Amberlyst^{R} as the catalyst under thermal conditions (Table 2).

In summary, we demonstrated that substituted anilines react with phenyliodonium ylides derived from 1,3-dicarbonyl compounds in the presence of a catalytic amount of BF$_3$·Et$_2$O, producing 2-*N*-phenylamino-3-hydroxybut-2-enoate derivatives, which serve as precursors for the synthesis of substituted indoles. The indoles could be prepared directly from anilines and phenyliodonium ylides under both thermal and photochemical conditions.

Acknowledgements

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Notes and references

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