The Synthesis of Polysubstituted Pyrroles *via* the Coupling of Phenyliodonium Ylides and Enamine Esters

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Abstract: The boron trifluoride etherate $(BF_3 \cdot Et_2O)$ -catalyzed reactions between phenyliodonium ylides and enamine esters provide an efficient method for the synthesis of polysubstituted pyrroles.

Keywords: coupling reactions; enamine esters; phenyliodonium ylides; pyrroles

Pyrroles constitute an important category of heterocyclic ring systems which exist in many naturally occurring products.^[1] Many pyrrole-containing compounds exhibit important biological and pharmaceutical activities,^[2] and are found to be of great utility in materials sciences.^[3] Consequently, great efforts have been made to find efficient synthetic methodologies to gain access to pyrroles.^[4] While many new synthetic approches toward the pyrrole skeleton have been established in recent years,^[5] it is still highly desirable to develop simple, convenient methods for the synthesis of polysubstituted pyrroles. Herein we wish to report a new protocol for the synthesis of polysubstituted pyrroles which employs the coupling reactions between phenyliodonium ylides and enamine esters.

Phenyliodonium ylides derived from 1,3-dicarbonyl compounds are useful synthetic imtermediates which have aroused much attention during the last decade.^[6] Phenyliodonium ylides can be transformed to carbenoids by the catalysis of transitional metals such as copper(I) and Rh(II), and subsequently undergo C–H insertion or addition to alkenes.^[7] On the other hand, the reactions of phenyliodonium ylides under metal-free conditions are far less explored. It was reported recently that phenyliodonium ylides could be coupled with electron-rich arenes in the presence of Lewis acids.^[8] Considering the electrophilic character of iodonium ylides, we envisioned that by using acids as

catalyst, electron-rich olefins such as enamine esters might also react with iodonium ylides, giving rise to coupling product \mathbf{A} , which could undergo further reactions to form pyrroles (Scheme 1). As both enamine esters and phenyliodonium ylides can be easily accessed from simple starting materials, it was expected that this strategy, if successful, would constitute a convenient approach for the synthesis of polysubstituted pyrroles.





To achieve this goal, firstly the reaction conditions were explored using iodonium ylide **1a** and enamine ester **2a** as the substrates, and the reaction was performed in CH₂Cl₂. To our delight, we found that, with several commonly used acids as the catalysts, the pyrrole product **3aa** was formed just as expected (Table 1). The best result was obtained when BF₃·Et₂O was used (Table 1, entry 2). The reaction was complete in just 10 min, and the yield of **3aa** reached 96%. By comparison, the reaction did not



Table 1. The reactions between 1a and 2a under various conditions.^[a]

0	0	CO ₂ CH ₃	H ₃ CO ₂ C	CO ₂ CH ₃
	OCH ₃ +	NH C	H ₂ Cl ₂	N Ph
1a (0.	2 mmol) 2a	(0.2 mmol)	3aa	
Entry	Catalyst (equiv.)	Reaction time	Conversion [%]	Yield [%] ^[b] of 3aa
1	none	2 days	trace	trace
2	$BF_3 \cdot Et_2O(0.2)$	10 min	100	96
3	CSA (0.2)	1 day	75	60
4	TfOH (0.2)	10 min	100	22
5	$Tf_2O(0.2)$	10 min	90	79
6	$CF_3COOH(0.2)$	1 hour	100	71
7	CuCl (0.2)	1 day	84	80
8	CuI (0.2)	1 day	80	73

^[a] The reactions were carried out in CH₂Cl₂ at room temperature.

^[b] Isolated yield.

take place in the absence of catalyst (Table 1, entry 1). Further experiments showed that the reaction proceeded well in several solvents, among which CH_2Cl_2 and acetonitrile led to the best results (Table 2). It is interesting to see that copper(I) salts could also catalyze the reaction, but the conversion was not complete even after one day (Table 1, entries 7 and 8).

Table 2. Solvent effects on the reaction between 1a and 2a.^[a]

Entry	Solvent	Reaction time [min]	Conversion [%]	Yield [%] ^[b] of 3aa
1	CH_2Cl_2	10	100	96
2	CHCl ₃	10	100	92
3	CH ₃ CN	10	100	96
4	CF ₃ CH ₂ OH	240	82	73
5	CH ₃ OH	240	80	68
6	THF	60	100	90
7	DMF	240	71	51

[a] The reactions were carried out at room temperature.
 [b] Isolated yield.

isolated yield.

This protocol could be used to synthesize a variety of differently substituted pyrroles, and the yields were generally high (Table 3). It is noteworthy that when iodonium ylide **1e** was used, pyrroles **3** was obtained as the single regioisomer (Table 3, entries 15–18). In the case of iodonium ylide **1f** which contains the labile chloromethyl group, pyrrole products were obtained as the mixture of 2-chloromethyl-substituted pyrroles (**3fh-1** and **3fm-1**) and their 2-hydroxymethyl-substituted counterparts (**3fh-2** and **3fm-2**) (Table 3, entries 19 and 20). Products **3fh-2** and **3fm-2** were probably generated as the result of *in situ* substitution of the chlorine atom by a hydroxy group after the pyrroles had formed, as **1f** was found to be stable to water. Although the substitution of the chlorine atom by a hydroxy group could not be avoided under the reaction conditions, the combined yields of the pyrrole products were quite high, demonstrating the mildness of the reaction conditions and the potential usefulness of the method for the synthesis of complex pyrrole structures.

In conclusion, a new method employing the coupling reactions of phenyliodonium ylides with enamine esters has been developed for the synthesis of polysubstituted pyrroles. This method is advantageous in terms of simplicity and mildness, and hopefully could find wide application in the synthesis of complex pyrrole-containing compounds.

Experimental Section

Phenyliodonium ylides $(1)^{[9]}$ and enamine esters $(2)^{[10]}$ were prepared according to the reported procedures.

General Procedure for the Reactions

To a mixture of enamine esters (2) (0.2 mmol) and iodonium ylides (1) (0.2 mmol) in CH_2Cl_2 , (0.5 mL) was added $BF_3 \cdot Et_2O$ (0.04 mmol), and the mixture was stirred at the room temperature under an argon atmosphere. After the reaction was finished as indicated by TLC, the mixture was concentrated under reduced pressure, and the residue was worked-up by flash column chromatography to give product **3**.

In a typical experiment, to a solution of 41 mg of **2a** (0.2 mmol) in CH₂Cl₂ (0.5 mL) were added 64 mg of **1a** (0.2 mmol). The suspension was stirred at room temperature under an argon atmosphere. Then 0.005 mL of BF₃·Et₂O (0.04 mmol) were added to the mixture. The reaction was finished in 10 min. The mixture was concentrated under reduced pressure, and the residue was worked-up with flash column chromatography (petroleum ether/EtOAc: 7/1) to give **3aa**; yield: 58 mg (96%).

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Table 3. Synthesis of pyrroles from phenyliodonium ylides (1) and enamine esters (2).^[a]





Entry]	Iodonium vlides			Enamine ester		Reaction time [min]	Product/Yield [%] ^[c]	
2	1	\mathbf{R}^1	\mathbb{R}^2	2	\mathbb{R}^3	\mathbb{R}^4	\mathbb{R}^5		[]
1	1 a	Me	OMe	2a	Me	Bn	Me	10	3aa /96
2	1 a	Me	OMe	2b	Me	<i>n-</i> Bu	Et	10	3ab /95
3	1 a	Me	OMe	2c	Me	allyl	Et	15	3ac /96
4	1 a	Me	OMe	2d	<i>n</i> -Pr	<i>n-</i> Bu	Et	10	3ad /96
5	1b	Me	OEt	2e	Ph	Н	Me	240	3be /70
6	1b	Me	OEt	2f	Me	Н	Me	240	3bf /74
7	1b	Me	OEt	2g	Me	Bn	Et	20	3bg /96
8	1c	Me	Me	2b	Me	<i>n</i> -Bu	Et	30	3cb /94
9	1c	Me	Me	2g	Me	Bn	Et	30	3cg /91
10	1c	Me	Me	2h	Me	allyl	Me	45	3ch /93
11	1c	Me	Me	2i	<i>n</i> -Pr	Bn	Et	20	3ci /91
12	1d	Ph	OEt	2h	Me	allyl	Me	20	3dh /84
13	1d	Ph	OEt	2j	Me	<i>n-</i> Bu	Me	20	3dj /85
14	1d	Ph	OEt	21	<i>n</i> -Pr	allyl	Et	30	3dl /92
15	1e	Me	Ph	2d	<i>n</i> -Pr	<i>n-</i> Bu	Et	30	3ed /91
16	1e	Me	Ph	2h	Me	allyl	Me	30	3eh /93
17	1e	Me	Ph	2j	Me	<i>n-</i> Bu	Me	35	3ej /97
18	1e	Me	Ph	21	<i>n</i> -Pr	allyl	Et	30	3el /89
19 ^[b]	1f	ClCH ₂	OEt	2h	Me	allyl	Me	10	3fh-1/36; 3fh-2/57
20 ^[b]	1f	ClCH_2^2	OEt	2m	Me	Ph	Me	10	3fm-1 /52; 3fm-2 /44

^[a] The reactions were carried out at room temperature.

^[b] The reactions were carried out at 0°C.

^[c] Isolated yields.

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