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Syntheses of Isochromenes and Naphthalenes by Electrophilic Cyclization of Acetylenic Arenecarboxaldehydes

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Abstract

Highly substituted 1*H*-isochromenes, isobenzofurans and pyranopyridines can be prepared by allowing *o*-(1-alkynyl)arenecarboxaldehydes and ketones to react with I₂, ICl, NIS, Br₂, NBS, *p*-O₂NC₆H₄SCl or PhSeBr, and various alcohols or carbon-based nucleophiles at room temperature. Naphthyl ketones and iodides are also readily prepared by the reaction of 2-(1-alkynyl)arenecarboxaldehydes with I₂ and simple olefins or alkynes.

Introduction

The electrophilic cyclization of functionally-substituted alkenes has provided an extremely useful route to a wide variety of heterocyclic and carbocyclic compounds, which have proven useful as intermediates in the synthesis of natural products and pharmaceuticals.¹ Analogous chemistry of alkynes has been far less studied, although it would appear to be a very promising route to an extraordinary range of useful, functionally-substituted heterocycles and carbocycles.² Our recent work and that of others have indicated that benzofurans,³ benzothiophenes,⁴ isoquinolines,⁵ indoles,^{3c,6} isocoumarins,⁷ isoindolinones,⁸ polycyclic aromatics⁹ and a number of other heterocycles¹⁰ can be easily synthesized by the electrophilic cyclization of appropriate functionally-substituted alkynes using iodine-, bromine-, sulfur- and selenium-containing electrophiles under exceptionally mild reaction conditions (Scheme 1).

Not long ago, Yamamoto reported an interesting cyclization of acetylenic aldehydes to 1-alkoxy-1*H*-isochromenes catalyzed by Pd(OAc)₂ (eq 1).¹¹ The Pd(II) salt employed was

claimed to exhibit a dual role as both a Lewis acid and a transition-metal catalyst. Recently, a similar preparation of 4-iodo-1*H*-isochromenes has been achieved upon reaction of bis(pyridine)iodonium tetrafluoroborate (IPy₂BF₄) and HBF₄ with the same acetylenic carbonyl precursors in the presence of various nucleophiles (eq 2).¹² The use of expensive

IPy₂BF₄ together with B(OMe)₃ or toxic, strongly acidic HBF₄, and the relatively complicated stepwise procedure employed have certain drawbacks synthetically. Furthermore, the full scope of this cyclization has yet to be reported.

We simultaneously found that this three component reaction¹³ proceeds smoothly by using the simple electrophiles ICl, NIS, Br₂, NBS, *p*-O₂NC₆H₄SCl and PhSeBr to generate the corresponding iodine-, bromine-, sulfur- and selenium-substituted heterocycles in high yields under very mild reaction conditions.¹⁴ Herein, we wish to report further details on this efficient approach to heterocycles and carbocycles involving electrophilic cyclization using a range of electrophiles and nucleophiles.

Results and Discussion

Our initial studies were aimed at finding optimal reaction conditions for the electrophilic cyclization of the *o*-(1-alkynyl)benzaldehydes. Our investigation began with the reaction of *o*-(phenylethynyl)benzaldehyde (**1**), methanol and I₂ (eq 3, Table 1). The reaction was first attempted using 0.25 mmol of *o*-(phenylethynyl)benzaldehyde (**1**), 1.2 equiv of methanol, 1.0 equiv of K₂CO₃ and 1.2 equiv of I₂ in CH₂Cl₂ at room temperature. Iodocyclization proceeded smoothly and provided an 88% yield of the desired product **2**. Other solvents, such as CH₃CN and DMF, were also investigated and proved to be far less effective. KHCO₃ and NEt₃ were also investigated as bases. While KHCO₃ provided a slightly lower yield of the desired product than K₂CO₃, NEt₃ proved to be totally ineffective and none of the desired product was detected. Although CH₂Cl₂ is not a good solvent for K₂CO₃, the presence of K₂CO₃ was crucial for a clean, high yielding reaction. K₂CO₃ is presumed to neutralize the by-product HI of the electrophilic cyclization, which can also react with the acetylenic aldehyde and generate the corresponding pyrilium salt.¹⁵ Increasing the amount of methanol from 1.2 equiv to using MeOH as the solvent actually resulted in a lower yield. 1.2 Equiv of I₂ has proven to be enough to achieve a high yield. Further increasing the amount of I₂ did not give any better yield. Based on the above optimization efforts, the combination of 1.2 equiv of nucleophile, 1.0 equiv of K₂CO₃, and 1.2 equiv of I₂ and using CH₂Cl₂ as the solvent at room temperature gave the best results. This procedure has been used as our standard reaction conditions for subsequent electrophilic cyclizations.

To explore the scope of this cyclization, other commercially available iodine, bromine, phosphorous, sulfur and selenium electrophiles have also been used in this process under similar reaction conditions. The results are summarized in Table 2. It has been found that I₂, NIS, ICl, NBS, PhSeBr and *p*-O₂NC₆H₄SCl are all good electrophiles for the reaction of 2-(phenylethynyl)benzaldehyde (**1**) and MeOH, providing decent yields of the desired cyclization products (entries 1–7). The strong electrophile Br₂ also readily reacted with aldehyde **1** to generate the desired cyclization product (entry 5). However, the reaction is not clean and only 21% of the desired product was obtained. Electrophiles, such as *tert*-butylsulfinyl chloride and diphenylphosphinous chloride (Ph₂PCl) did not react with aldehyde **1** and none of the desired product was observed (entries 8 and 9).

To further explore the scope of this chemistry, various nucleophiles have been tested in this process using 2-(phenylethynyl)benzaldehyde (**1**) and I₂. Alcohols, such as MeOH, *n*-BuOH, *t*-BuOH and 2-iodobenzyl alcohol, all react well and provide good to excellent yields of the desired iodocyclization products (entries 1 and 10–12). The reaction with *t*-BuOH provided only a modest yield due apparently to the steric hindrance of the *tert*-butyl group or perhaps dehydration of this alcohol (entry 11).

Nucleophiles other than alcohols have also been examined under our standard cyclization conditions. While the reaction using *N,N*-dimethylaniline as the nucleophile provided an

excellent yield of the cyclization product (entry 13), those using phenol, thiophene, *N*-methylindole, 5,5-dimethyl-1,3-cyclohexanedione and 1,3-cyclohexanedione only afforded modest yields of the desired cyclization products (entries 14–18). The reaction with phenol provided both carbon and oxygen trapping products (entry 14). The reactions which have produced carbon coupling products were highly regioselective. The 1,3-diketone reactions gave enol trapping products, plus some aldol product in the case of 5,5-dimethyl-1,3-cyclohexanedione (entries 17 and 18). The reaction with the trimethylsilyl enol ether of acetophenone did not afford the desired cyclization product under our standard reaction conditions; only the aldol condensation product was observed. However, adding 1 equiv of KF as a promoter greatly affected the reaction pathway, affording a 63% yield of the desired cyclization product (entry 19). Other nucleophiles, such as benzofuran, benzylthiol, Meldrum's acid and 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene failed to react under our standard reaction conditions and none of the desired products were observed (entries 20–23). Thiols did not prove to be useful nucleophiles, perhaps due to oxidation to disulfides by iodine. Primary and secondary amines have also been used as nucleophiles, but none of the expected products were formed.

To further examine the generality of this chemistry, acetylenic aldehydes bearing different substituents on the carbon-carbon triple bond were synthesized in high yields by palladium/copper-catalyzed coupling of the appropriate *o*-bromoarene carboxaldehydes and the corresponding terminal alkynes.¹⁶ The resulting acetylenic aldehydes were then allowed to react under our standard electrophilic cyclization conditions to afford the corresponding 1*H*-isochromene products. Alkynes bearing an alkyl and a vinylic substituent on the triple bond also react well and provide the desired electrophilic cyclization products in good yields, when methanol and *N,N*-dimethylaniline are used as the nucleophiles (entries 24, 25, 27, 28 and 30). 4,5-Dimethoxy-2-(phenylethynyl)benzaldehyde (**25**) also underwent smooth iodocyclization, providing a quantitative yield of the MeOH trapped product (entry 31).

Besides the successful use of PhSeBr as an electrophile (entry 6, Table 2), we have also been able to extend this cyclization chemistry to sulfur electrophiles. Thus, aryl-, alkyl-, and vinylic-substituted acetylenes undergo cyclization and provide sulfur-substituted isochromenes in 60–74% yields respectively (entries 7, 26 and 29). The reaction of aldehyde **25** and *p*-O₂NC₆H₄SCl afforded only a 51% yield of the desired cyclization product, alongside a 45% yield of the product of simple addition of the electrophile to the carbon-carbon triple bond (entry 32).

Rather unstable 2-Ethynylbenzaldehyde (**28**) and 2-(trimethylsilylethynyl)benzaldehyde (**29**) have also been employed as aldehydes, but they did not undergo cyclization when MeOH and I₂ were used (entries 33 and 34). The reactions were messy and unidentifiable mixtures were observed instead.

Pyridinecarboxaldehyde derivatives **30** and **32** have also been allowed to react under our standard cyclization conditions using MeOH as a nucleophile and I₂ or ICl as electrophiles. The electron-deficient aromatic ring of these aldehydes did not affect cyclization. We still obtained the desired iodocyclization products using aldehyde **30** and either I₂ or ICl in 70% and 64% yields respectively (entries 35 and 36). The presence of an electron-donating group on the aromatic ring on the distal end of the carbon-carbon triple bond greatly enhanced the cyclization and a 96% yield of the desired cyclization product was obtained when pyridinecarboxaldehyde **32** was employed (entry 37).

Besides aromatic carboxaldehydes, vinylic carboxaldehyde **34** has also been examined under our standard iodocyclization conditions. Using I₂ and methanol, a 1:1 mixture of 5- and 6-membered ring products was observed by ¹H NMR spectroscopic analysis (entry 38). Using

NIS and *n*-BuOH, a mixture was again obtained, but this time the 5-membered ring product was favored by a 7:1 ratio (entry 39). The ratio of 5- to 6-membered ring products thus varies depending on the nucleophile and electrophile used in the reaction.

We have also investigated the possibility of carrying out a double iodocyclization, which might be quite useful for the quick assembly of systems with extended conjugation. Compound **39** underwent smooth iodocyclization to afford the double cyclization product in a 75% yield (entry 40). In all cases where we have compared results, these reactions with readily available, inexpensive iodine have given higher yields than the corresponding process using the expensive iodonium salt and HBF₄ reported by Barluenga.¹²

We have also examined the cyclization of a ketone-containing alkyne. Ketone **41** has been allowed to react with I₂ and methanol under our standard reaction conditions (entry 41). This reaction proceeded smoothly to provide a 90% yield of a 5-*exo-dig* cyclization product, rather than the 6-membered ring ether formed by the electrophilic cyclization of analogous benzaldehyde derivatives. The use of K₂CO₃ in our standard procedure provides very mild basic conditions and avoids the acid-initiated, partial decomposition of this cyclization product described by Barluenga.¹²

Interestingly, we were unable to get high yields of the desired iodocyclization products when we employed our reagents in a stepwise manner analogous to that described by Barluenga.¹² Instead, an unreactive solid, presumed to be the pyrilium salt,¹⁵ was generated. Based on this observation, a possible mechanism for our process is proposed in Scheme 2. We believe that these cyclizations proceed by *anti* attack of the electrophile and the carbonyl to produce a pyrilium intermediate. Before it forms an insoluble precipitate,¹⁵ the pyrilium intermediate is immediately trapped by the nucleophile present in the reaction mixture.

Recently, a number of new naphthalene synthesis have been reported, which involve alkyne cyclizations.¹⁷ For example, Barluenga *et al* have reported that IPy₂BF₄, *o*-alkynyl-substituted carbonyl compounds, and alkynes react to give 1-iodonaphthalene derivatives and the reaction with alkenes instead of acetylenes afforded related naphthyl ketone derivatives.^{17d} Our studies have shown that the same substituted naphthalenes can be synthesized in high yields comparable to those obtained by Barluenga employing our I₂ procedure and alkenes or alkynes as the trapping reagent (Scheme 3). The use of the more sophisticated iodonium reagent IPy₂BF₄ employed by Barluenga^{17d} for this same process is not necessary. These reactions are believed to proceed through a similar pyrilium intermediate, which is trapped by the alkene or alkyne. Once again, the use of readily available, easily handled I₂ greatly simplifies the procedure developed by Barluenga.^{17d}

We believe that this approach to heterocycles should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting halogen, sulfur and selenium functionalities into other substituents. For instance, the resulting heterocyclic iodides should be particularly useful intermediates in many palladium-catalyzed processes, such as Sonogashira,¹⁶ Suzuki,¹⁸ Stille,¹⁹ and Heck²⁰ cross-couplings. For instance, compound **2** has been treated under standard Heck and Suzuki conditions, providing the corresponding coupling products **46** and **47** in 99% and 79% yields respectively (Scheme 4). Using the palladium-catalyzed annulation of an internal alkyne developed in our group,²¹ we have been able to convert compound **2** to **48** in a 92% yield. Compound **2** is also readily oxidized to 4-iodoisocoumarin **49** in an 81% yield by using PCC (Scheme 4).

Conclusions

Efficient syntheses of a variety of substituted oxygen-containing heterocycles and carbocycles have been developed using the electrophilic cyclization of acetylene-containing aldehydes and

ketones and the generality of this process has been explored. This method accommodates various functional groups and affords substituted heterocycles in good to excellent yields. The resulting iodoheterocycles are readily elaborated to more complex compounds by using known organopalladium chemistry. Although Barluenga^{12,17d} reported similar reactions using *o*-(1-alkynyl)benzaldehydes and IPy₂BF₄ plus HBF₄, we have been able to extend the above chemistry to polycyclic compounds and bisisochromenes using readily available, inexpensive, easily handled I₂ as the iodine source, and we have generally obtained cleaner and higher yielding reactions. We have also shown that electrophiles, such as ICl, NIS, NBS, Br₂, *p*-O₂NC₆H₄SCl and PhSeBr, can be used in this chemistry.

Experimental Section

General

¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm) or a basic KMnO₄ solution [3 g of KMnO₄ + 20 g of K₂CO₃ + 5 mL of NaOH (5 %) + 300 mL of H₂O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a triple quadrupole mass spectrometer. High resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents

All reagents were used directly as obtained commercially unless otherwise noted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Table 1

Iodocyclization of 2-(phenylethynyl)benzaldehyde

solvent	MeOH (equiv)	I ₂ (equiv)	base (equiv)	yield (%)
CH ₂ Cl ₂	1.2	1.2	K ₂ CO ₃ (1.0)	88
CH ₃ CN	1.2	1.2	K ₂ CO ₃ (1.0)	40
DMF	1.2	1.2	K ₂ CO ₃ (1.0)	trace
CH ₂ Cl ₂	1.2	1.2	KHCO ₃ (1.0)	70
CH ₂ Cl ₂	1.2	1.2	Et ₃ N	-
CH ₂ Cl ₂	2.0	2.5	K ₂ CO ₃ (1.0)	80
CH ₂ Cl ₂	2.0	2.5	K ₂ CO ₃ (2.0)	78
MeOH	-	2.5	K ₂ CO ₃ (2.0)	68

Table 2

Electrophilic cyclization of acetylenic aldehydes, ketones and imines^a

entry	alkyne	nucleophile	electrophile	product	isolated yield (%)
1		MeOH	I ₂		93 ^b
2		MeOH	NIS		60
3		MeOH	ICI		74
4		MeOH	NBS		51
5		MeOH	Br ₂		21
6		MeOH	PhSeBr		65
7		MeOH	<i>p</i> -O ₂ NC ₆ H ₄ SCl		74
8		MeOH			-
9		MeOH			-

entry	alkyne	nucleophile	electrophile	product	isolated yield (%)
10		<i>n</i> -BuOH	I ₂		81
11		<i>t</i> -BuOH	I ₂		49
12			I ₂		87
13			I ₂		88
14			I ₂		35 ^c

entry	alkyne	nucleophile	electrophile	product	isolated yield (%)
15			I ₂		43
16			I ₂		30 ^d
17			I ₂		53:35
18			I ₂		54 ^d

entry	alkyne	nucleophile	electrophile	product	isolated yield (%)
19			I ₂		63 ^e
20			I ₂		-
21			I ₂		-
22			I ₂		-

entry	alkyne	nucleophile	electrophile	product	isolated yield (%)
23			I ₂		-
24		MeOH	I ₂		84
25			I ₂		70
26		MeOH	<i>p</i> -O ₂ NC ₆ H ₄ SCl		73
27		MeOH	I ₂		81
28		MeOH	ICl		53

entry	alkyne	nucleophile	electrophile	product	isolated yield (%)
29		MeOH	<i>p</i> -O ₂ NC ₆ H ₄ SCl		60
30			I ₂		83
31		MeOH	I ₂		100
32		MeOH	<i>p</i> -O ₂ NC ₆ H ₄ SCl		51 ^f
33		MeOH	I ₂	-	-
34		MeOH	I ₂	-	-

entry	alkyne	nucleophile	electrophile	product	isolated yield (%)
35		MeOH	I ₂		70
36		MeOH	ICl		64
37		MeOH	I ₂		96
38		MeOH	I ₂		60 ^d (1:1)
39		<i>n</i> -BuOH	NIS		39 ^d (1:7)
40		MeOH	I ₂		75

entry	alkyne	nucleophile	electrophile	product	isolated yield (%)
41		MeOH	I ₂		42
					90

^aThe reactions were run under the following conditions, unless otherwise specified. While stirring a solution of 2.5 mL of CH₂Cl₂ containing 0.25 mmol of the alkyne, 0.30 mmol of K₂CO₃, 0.30 mmol of electrophile were added and the resulting mixture was further stirred at room temperature until the total disappearance of the starting material upon TLC analysis.

^bThe reaction was run on a 1.0 mmol scale; the 0.25 mmol scale reaction provides an 88% yield of compound **2**.

^cA 25 % yield of *O*-trapping product was also observed.

^dThis yield was determined by ¹H NMR spectroscopic analysis due to the apparent instability of the product.

^e1 Equiv of KF was added.

^fA 45% yield of adduct formed by direct addition of *p*-O₂NC₆H₄SCl to the triple bond was obtained.