Heteroatom Chemistry
Volume 18, Number 3, 2007

Triphenylphosphine Catalyzed Formation of Functionalized 2-Aminothiophenes

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Received 7 March 2006; revised 8 September 2006

ABSTRACT: *Triphenylphosphine was used as a nucleophilic catalyst in the addition–cyclization reaction of phenyl isothiocyanate with electron-deficient allenes. This strategy offers a new approach for the synthesis of 2-aminothiophenes under neutral conditions.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:312–315, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20300

INTRODUCTION

Illustrated by effective synthetic methods, organocatalysis is emerging as a rapidly growing field of organic chemistry. The new powerful processes allow a wide range of applicative methods for carbon—carbon bond formation, sometimes with remarkable stereoselectivities. Trivalent organophosphorus compounds are very effective nucleophiles, which offer a broad interest in either equimolar or catalytic conditions, as recently demonstrated by the Morita–Baylis–Hillman reaction.

So the development of new synthetic methods to functionalize or to build heterocycles, merely using both tandem reactions and nucleophilic organocatalysis is still a question of interest. Some years ago, Cristau et al. reported the potential of allenes bearing an electron-withdrawing group for the preparation of some heterocycles via a sequential multistep synthesis using stoichiometric quantity of triphenylphosphine [1]. The catalytic version was expanded until recently to a large group of electrophile–pronucleophiles such as Michael olefins [2], imines [3], and aldehydes [4] for the synthesis of cyclopentenes 2,5-dihydropyrroles and 1,3-dioxan-4-ylidenes, respectively. According to this strategy, heterocumulenes can react as electrophile–pronucleophiles with allenes. In this study, we have investigated the reactivity of phenyl isothiocyanate and discussed the preliminary results of its addition to electron-deficient allenes catalyzed by triphenylphosphine, thus allowing an original access to scarcely accessible 2-aminothiophenes [5].

RESULTS AND DISCUSSION

The reaction of phenyl isothiocyanate (**1**) with allenic esters [6] or ketones **2a–d** [7] in the presence of triphenylphosphine afforded functionalized 2-aminothiophenes **3a–c** (Scheme 1).

Mechanism

A mechanism for the formation of 2-aminothiophenes **3** is proposed in Scheme 2. The catalytic cycle is initiated by a nucleophilic addition of triphenylphosphine to the electron-deficient allene **2** with the formation of the enolate-vinylphosphonium intermediate **4a, b** (step 1). This nucleophilic species formed in situ can then add to the electrophilic carbon atom of the phenyl isothiocyanate to produce a new nucleophilic intermediate **5** (step 2). The iminothiolate **5a** is the reactive form. The next step involves an intramolecular 5-*endo-trig* cyclization to

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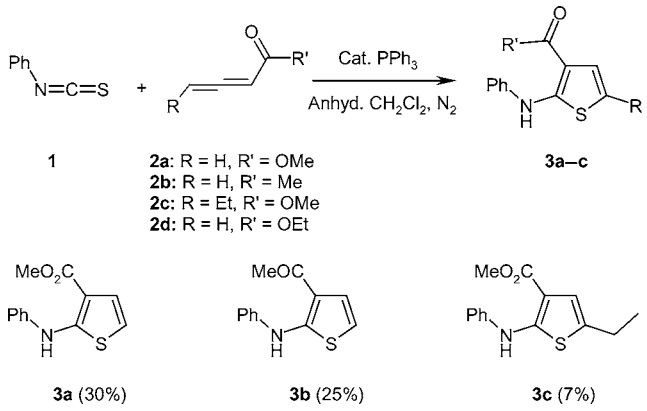


SCHEME 1 Synthesis of 2-aminothiophenes **3a–c**.

furnish the cyclic structure **6** (step 3) in equilibrium with **7** (step 4). Finally, elimination and regeneration of the triphenylphosphine catalyst afford **8** (step 5), which spontaneously aromatizes into thiophene **3** by prototropy.

Isolated yields (7–30%) remained low in all tested conditions. Adding methyl 2,3-butadienoate (**2a**) or acetylallene (**2b**) (2 equiv) to a mixture of phenyl isothiocyanate (1 equiv) and PPh_3 (1 or 0.1 equiv), the corresponding 2-aminothiophenes **3a, b** were formed in respectively 30% and 25% yields (Table 1, entries 2 and 4).

The addition of a large excess of ethyl 2,3-butadienoate (**2d**) or acetylallene (**2b**) (8 equiv) did not improve the yields, and led exclusively to the oligomerization of allenes in a complex mixture (entries 3 and 5).

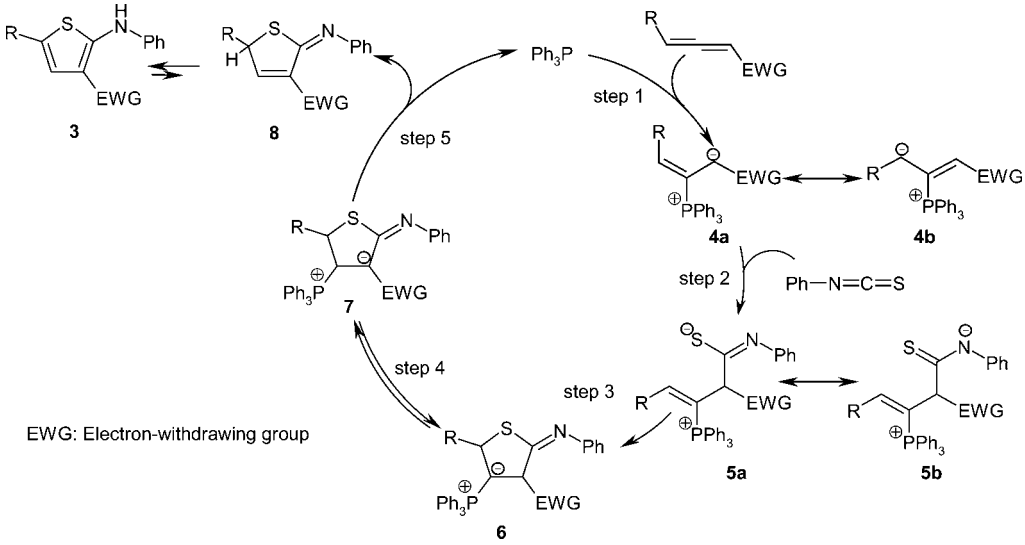
Finally, using a γ-substituted allenoate **2c**, a lower yield (7%, Table 1, entry 9) of the desired product **3c** was obtained. The isomerization of the allene into the corresponding diene was the main reaction [8].

In all reactions, oligomerization and polymerization of allene indicated the weakest reactivity of the isothiocyanate moiety than the allene itself. Therefore, the activation of phenyl isothiocyanate with a Lewis acid was examined. As listed in Table 2, neither $ZnCl_2$ nor $LiClO_4$ improved the conversion of the phenyl isothiocyanate into **3b** (entries 1 and 5). The use of copper(I) salts [$CuCl(PPh_3)_3$] and CuBr as soft Lewis acids did not favor the formation of **3b** because of the complexation of copper by triphenylphosphine (entries 2–4). In these conditions, even the oligomerization of allene was considerably slowed down.

In conclusion, we have described the potential of a heterocumulene (phenyl isothiocyanate) and electron-deficient allenes in an unusual tandem addition–cyclization and aromatization process catalyzed by triphenylphosphine. This nucleophilic organocatalysis represents a new approach for the elaboration of the 2-aminothiophene backbone.

EXPERIMENTAL

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out under nitrogen in flame-dried glassware. Reagents and solvents were purified before use and stored under nitrogen atmosphere. All reactions were monitored by GC/MS, ^{31}P NMR, or ^{1}H NMR. Flash column chromatography was performed using E. Merck silica gel 60 (35–70 μm) and compressed air.



SCHEME 2 Mechanism of formation for 2-aminothiophenes **3**.

TABLE 1 Synthesis of 2-Aminothiophenes **3a–c** in Various Conditions

Entry	**2** *(equiv)*	*PPh_3 (equiv)*	*Conditions*	**3** Yield (%)[a]
1	**2a** (1)	1	−30°C to −15°C, 18 h	10
2	**2a (2.3)**	**1**	**−10°C, 3 h, then 20°C**	**30**
3	**2d** (8)	0.1	20°C, 48 h	0
4	**2b (2)**	**0.1**	**20°C, 24 h**	**25**
5	**2b** (8)	0.1	20°C, 48 h	0
6	**2b** (0.75)	0.5	20°C, 24 h	22
7	**2b** (2)	0.1	Toluene, 20°C, 16 h	(16)[b]
8	**2b** (2)	0.1	Reflux, 7 h	(15)[b]
9	**2c (1)**	**0.5**	**−10°C, 18 h**	**7**
10	**2c** (1.1)	0.1	20°C, 24 h	Traces

[a]Isolated yields.
[b]Yields given in brackets were measured by GC/MS in the reaction mixture, with 2,4,6-trimethoxybenzene as internal reference.
Entries 2, 4 & 9 in bold represent the best reaction conditions for the products as described in Experimental section.

Melting points were determined with an Electrothermal Digital Melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1000 Fourier transform spectrometer. ^1H and ^{13}C spectra were recorded on a Bruker Avance 250 spectrometer. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane, and coupling constants (J) are given in hertz. Assignments were made using a combination of 1D and 2D spectra (COSY). Mass spectra were run on a Jeol JMS DX-300 spectrometer (positive FAB ionization and exact mass measurements using *p*-nitrobenzyl alcohol matrix). Elemental analyses were performed on a THERMOFINNIGAN Flash EA 1112 apparatus.

General Procedure for the Synthesis of 2-Aminothiophenes **3a–c**

To a mixture of phenyl isothiocyanate (0.3 mol L^{-1}, 1 equiv) and PPh_3 (0.1–0.5 equiv) in anhydrous CH_2Cl_2, a solution of allene (0.7 mol L^{-1}, 2.3 equiv) in anhydrous CH_2Cl_2 was added dropwise over a period of 3 h at −10°C or 20°C under nitrogen atmosphere. After 24 h, the solvent was evaporated under reduced pressure and the product was purified by flash chromatography on silica gel.

*Methyl 2-phenylaminothiophen-3-yl-carboxylate (***3a***)* was prepared from phenyl isothiocyanate (1 equiv, 653 mg), Ph_3P (1 equiv, 1.27 g), and methyl buta-2,3-dienoate (2.3 equiv, 1.08 g). The product was eluted with hexane/ethyl acetate (100:0, and then 98:2) on silica gel. Yield: 30%, colorless oil; FT-IR (KBr): ν cm^{-1}) 3277 (NH), 3200, 3093, 2949, 1670 (C=O), 1594, 1557; ^1H NMR (250 MHz, $CDCl_3$) δ 3.90 (s, 3H, CH_3), 6.33 (d, $^3J = 5.7$ Hz, 1H, ^{4}CH), 7.10 (tt, $^3J = 7.0$ Hz, $^4J = 1.5$ Hz, 1H, $^{(4'-Ar)}$CH), 7.18 (d, $^3J = 5.7$ Hz, 1H, ^{5}CH), 7.37 (m, 4H, $^{(2'-Ar)}$CH + $^{(3'-Ar)}$CH), 9.94 (bs, 1H, NH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 51.61 (CH_3), 107.44 (^{5}CH), 107.87 (^{3}C), 118.58 ($^{(2'-Ar)}$CH), 123.32 (^{4}CH), 125.81 ($^{(4'-Ar)}$CH), 129.91 ($^{(3'-Ar)}$CH), 141.29 ($^{(1'-Ar)}$C), 158.89 (^{2}C), 166.74 (CO); MS(FAB+) (NBA): m/z (%) = 234 (52) [$M^+ + H$], 233 (100) [M^+], 202 (50) [$M^+ - OCH_3$]; FAB(+) HRMS: calcd. for $C_{12}H_{11}NO_2S$ 233.0511; found 233.0497.

*3-Acetyl-2-phenylaminothiophene (***3b***)* was prepared according to the general procedure using phenyl isothiocyanate (1 equiv, 0.99 g), Ph_3P (0.1 equiv, 193 mg), and acetylallene (2 equiv, 1.21 g). The product was eluted with hexane/dichloromethane (98:2) and then hexane/ethyl acetate (98:2) on silica gel. Yield: 25%, solid, mp 63°C; FT-IR (KBr): ν (cm^{-1}) 3300 (NH), 3103, 3083, 1616 (C=O), 1591, 1553, 1514, 1501; ^1H NMR (250 MHz, $CDCl_3$) δ 2.50 (s, 3H, CH_3), 6.30 (dd, $^3J = 5.8$ Hz, $^5J = 0.9$ Hz, 1H, ^{4}CH), 7.11 (tt, $^3J = 7.2$ Hz, $^4J = 1.2$ Hz, 1H,

TABLE 2 Effect of Lewis Acids

Entry	**2b** *(equiv)*	*PPh_3 (equiv)*	*Lewis Acid (equiv)*	*Conditions*	**3b** Yield (%)[a]	*Conversion (%)*[a] **1**	*Conversion (%)*[a] **2b**
1	2	0.1	$ZnCl_2$ (0.1)	20°C, 24 h	Traces	–	–
2	2	–	$[CuCl(PPh_3)_3]$ (0.2)	20°C, 16 h	24	26	100
3	4	–	$[CuCl(PPh_3)_3]$ (0.2)	20°C, 3 days	17	18	100
4	2	0.1	CuBr (1)	20°C, 20 h	0	0	4
5	2	0.1	$LiClO_4$ (0.1)	Et_2O_{anh}, 20°C, 16 h	1	6	80

[a]Yields and conversions were measured by GC/MS in the reaction mixture, with 2,4,6-trimethoxybenzene as internal reference.

$^{(4'-Ar)}$CH), 7.12 (d, $^3J = 5.8$ Hz, 1H, ^{5}CH), 7.38 (m, 4H,$^{(2'-Ar)}$ CH + $^{(3'-Ar)}$CH), 11.48 (bs, 1H, NH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.26 (CH_3), 106.91 (^{5}CH), 116.80 (^{3}C), 118.68 ($^{(2'-Ar)}$CH), 123.38 (^{4}CH), 125.82 ($^{(4'-Ar)}$CH), 129.48 ($^{(3'-Ar)}$CH), 140.53 ($^{(1'-Ar)}$C), 159.50 (^{2}C), 193.68 (CO); MS(FAB+) (NBA): m/z (%) = 217 (58) [M^+], 202 (10) [M^+—CH_3]; elemental analysis: calcd. (%) for $C_{12}H_{11}NOS$ 217.29; C 66.33, H 5.10; found: C 65.90, H 5.17.

Methyl 5-ethyl-2-phenylaminothiophen-3-yl-carboxylate (**3c**) was prepared from phenyl isothiocyanate (1 equiv, 994 mg), Ph_3P (0.5 equiv, 989 mg), and methyl hexa-2,3-dienoate (1 equiv, 928 mg). The product was eluted with hexane/ethyl acetate (100:0, and then 98:2) on silica gel. Yield: 7%, colorless oil; FT-IR (KBr): ν (cm^{-1}) 3275 (NH), 3214, 3065, 2966, 2937, 2851, 1669 (C=O), 1594, 1554; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, $^3J = 7.5$ Hz, 3H, CH_3), 2.71 (qd, $^3J = 7.5$ Hz, $^4J = 1.1$ Hz, 2H, CH_2), 3.87 (s, 3H, CH_3), 6.82 (t, $^4J = 1.1$ Hz, $^5J = 1.1$ Hz, 1H, ^{4}CH), 7,06 (tt, $^3J = 7.0$ Hz, $^4J = 1.4$ Hz 1H, $^{(4'-Ar)}$CH), 7.36 (m, 4H, $^{(2'-Ar)}$CH + $^{(3'-Ar)}$CH), 9.82 (bs, 1H, NH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 15.37 (CH_3), 22.95 (CH_2), 51.05 (CH_3), 106.55 (^{3}C), 118.01 ($^{(2'-Ar)}$CH), 120.19 (^{4}CH), 122.63 ($^{(4'-Ar)}$CH), 128.40 (^{5}C), 129.40 ($^{(3'-Ar)}$CH), 140.97 ($^{(1'-Ar)}$C), 156.97 (^{2}C), 166.22 (CO); F MS(FAB+) (NBA): m/z (%) = 262 (82) [$M^+ + H$], 261 (100) [M^+], 230 (68) [M^+—OCH_3], 214 (35) [M^+—OCH_3-$CH_3 + 1$]; FAB(+) HRMS: calcd. for $C_{14}H_{15}O_2NS$ 261.0824; found 261.0822.

ACKNOWLEDGMENTS

The authors acknowledge the Ministère de la Recherche, de la Jeunesse et de la Technologie for financial support (MRT fellowship).

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