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Facile synthesis of substituted thiophenes via Pd/C-mediated sonogashira coupling in water☆

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Abstract—The first successful Pd/C-mediated Sonogashira coupling of iodothiophene with terminal alkynes in water is described here. Pd/C-CuI-PPh_3 was found to be an efficient catalyst system for this coupling reaction. Using this economic and reliable process a variety of acetylenic thiophenes with a wide range of functional groups were prepared in good yields. Synthetic applications and in vitro anticancer properties of some of the compounds synthesized are described.

The pair benzene/thiophene represents one of the most prominent examples of bioisosterism[1] (bioisosteres are isosteric[2] molecules that have similar or antagonistic properties in biological systems) and therefore the synthesis of thiophene analogues has attracted considerable attention especially in pharmaceutical research. The exploratory replacement of a benzene ring in successful drugs by a thiophene moiety has become a routine strategy in modern drug design and development. The physiological effects of thiophene are similar to those of benzene (bioisostere), with frequently superior pharmacodynamic, pharmacokinetic, or toxicological properties. For example, thiophene replacement of the annulated benzene ring in derivatives of piroxicam, an anti-inflammatory agent used in arthritis patients, had no effect on activity.[3] Similarly, the thiophene analogue of amphetamine retains complete amphetamine-like activity.[4] Nevertheless, thiophene derivatives have shown numerous biological activities such as nematocidal,[5] insecticidal,[6] antibacterial,[7] antifungal,[8] and antiviral[9] activity. Recently, acetylenic thiophenes have been shown to possess good anti-inflammatory activities in rats.[10] In view of reported biological activities of alkynyl substituted heterocycles[11] and our effort in the synthesis of thiophene derivatives[12] of potential pharmacological significance we became interested in the synthesis of alkynyl substituted thiophenes. Due to the known anticancer activities of thiophene derivatives[13] as well as alkynes[11a–g] we anticipated that a combination of both in an appropriately substituted alkynylthiophene might show similar pharmacological properties. Herein, we report the synthesis and in vitro anticancer activities of alkynylthiophenes. Notably, development of alkynylthiophene as potential anticancer agents has not been explored earlier.

Transition metal-mediated cross-couplings have proven to be powerful tools for mild, highly efficient carbon–carbon bond formations. Among these processes, those involving palladium catalysis especially Sonogashira coupling or alkynylation of aryl halides[14] are particularly useful for the synthesis of complex molecules, owing to excellent levels of selectivity and high functional group compatibility. Sonogashira coupling or its modified form has been used successfully for the preparation of a variety of alkynylthiophenes.[15] This includes the coupling of terminal alkynes with halothiophene[15a,b] or 2-(butyltelluro) thiophene[10] or coupling of lithium alkynyl diisopropoxy borates with iodothiophene.[15c] A major problem associated with the conventional Sonogashira coupling is the use of large excess of secondary or tertiary alkyl amines as a solvent or co-solvent that

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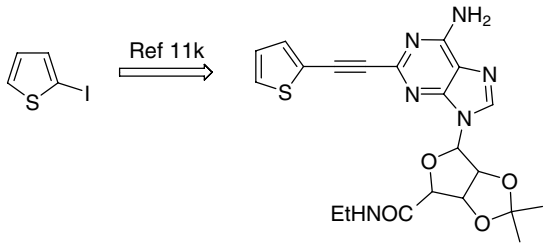
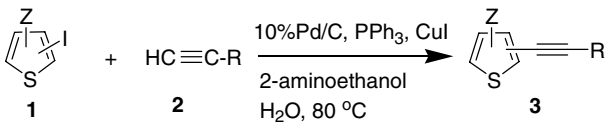


Figure 1. Synthesis of 2-thienyl derivative as selective A_{2a} adenosine receptor agonists.

often leads to environmental pollution. To overcome this problem we have recently developed a highly convenient method for the alkynylation of aryl halides under Pd/C-Cu catalysis using 2-aminoethanol as a base in water.[16] While a number of aryl halides were examined in our previous study the use of heteroaryl halides especially halothiophene has never been explored. Considering palladium-catalyzed alkynylation reactions based upon a thiophene scaffold could be an attractive strategy toward the synthesis of substituted thiophenes of potential biological significance[111] (Fig. 1), we chose to investigate the coupling of a wide array of terminal alkynes with iodothiophene in water. We reasoned that this aqueous version might have advantages over the conventional Sonogashira procedure and would provide flexible and rapid access to the substituted thiophenes.

To determine the feasibility of this approach, 2-iodothiophene (**1**) was treated with terminal alkynes (**2**, R = alkyl, hydroxyalkyl, aryl, etc.) in water in the presence of 10% Pd/C (0.026 equiv), PPh_3 (0.20 equiv), CuI (0.05 equiv), and 2-aminoethanol (3 equiv) under nitrogen. The reaction proceeded well and alkynylthiophenes were obtained in good to excellent yields (Scheme 1).[17] The results are summarized in Table 1.

Initially, we used our previous method[16] that involved the use of 0.04 equiv of 10%Pd/C for the coupling of 2-iodothiophene (**1a**) with 2-methyl-3-butyn-2-ol (**2a**) and the desired product **3a** was isolated in 85% yield (entry 1, Table 1). However, in the subsequent experiments we observed that the use of lesser quantity, that is, 0.03 or 0.026 equiv of Pd/C, did not affect the product yield (entries 2 and 3, Table 1). Therefore, to make the process more economical we decided to use 0.026 equiv of Pd/C in all other experiments as listed in Table 1. As outlined in Table 1, 2-iodothiophene (**1a**) showed good reactivity toward the present coupling reaction and a variety of terminal alkynes were employed under the condition studied (entries 4–15, Table 1). Various functional groups including hydrophobic and hydrophilic substitutents, for example, aryl, alkyl, hydroxy, ether, etc., present in the terminal alkynes were well tolerated.



Scheme 1. Pd/C-mediated alkynylation of iodothiophenes in water.

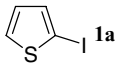
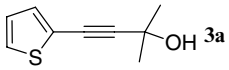
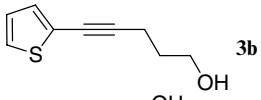
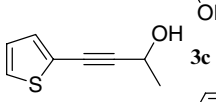
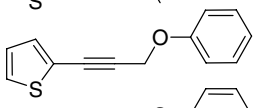
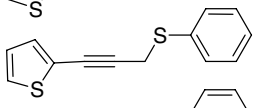
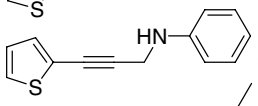
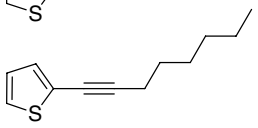
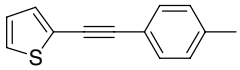
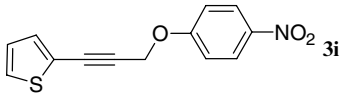
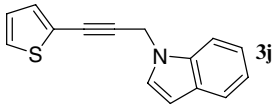
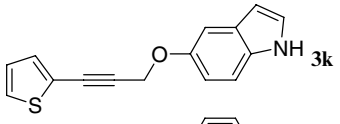
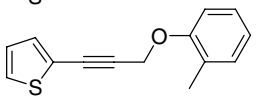
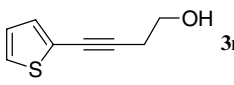
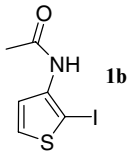
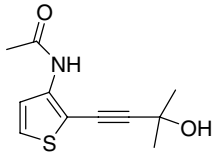
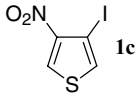
This allowed the preparation of a variety of 2-alkynylthiophenes (**3a**–**m**) under mild condition. Generally, yields of products were not affected by the nature of alkyne used. The use of other iodothiophene derivatives having electron-donating or -withdrawing groups, for example, *N*-(2-iodo thiophen-3-yl)acetamide (**1b**) and 3-iodo-4-nitrothiophene (**1c**), was also investigated and both of them afforded good yield of desired products when coupled with 2-methyl-3-butyn-2-ol under the condition employed (entries 16 and 17, Table 1).

While 2-iodothiophene (**1a**) is commercially available *N*-(2-iodo thiophen-3-yl)acetamide (**1b**) was prepared according to the literature method.[18a] 3-Iodo-4-nitrothiophene (**1c**) was prepared from commercially available 3-iodothiophene by using nitric acid and sulfuric acid mixture. All the terminal alkynes used are either commercially available or prepared[18b] according to Scheme 2.

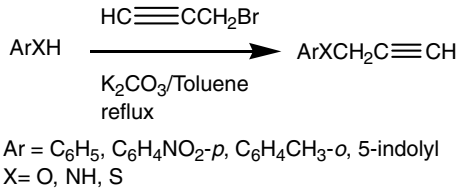
Compared with the previous work,[16] the present reaction required lesser equivalent of Pd/C, which suggested higher reactivity of 2-iodothiophene than iodobenzene toward the Pd catalyst under the condition studied. The electron-withdrawing inductive effect of sulfur at the nearby position perhaps aided the higher reactivity shown by 2-iodothiophene. Nevertheless, mechanistically the reaction seems to proceed according to a typical Sonogashira pathway where participation of 2-aminoethanol facilitated the coupling in aqueous media.[19] Having established 10% Pd/C-CuI-PPh_3 as an efficient catalyst system for the coupling of iodothiophene with terminal alkynes in water we decided to explore the synthetic application of alkynylthiophenes prepared by using this methodology. Thus compound **3m** was converted to the 4-hydroxy-1-thiophen-2-yl butan-1-one (**4**) and finally to the corresponding acid (**5**) as shown in Scheme 3. The acid can be converted to the cyclic ketone **6** (6,7-dihydrobenzo[*b*]thiophene-4(5*H*)one or 4-keto-4,5,6,7-tetrahydrothianaphthene) via reduction followed by cyclization of the resulting acid chloride according to the known method.[20] The present route therefore provides an useful and alternative access to the ketone **6**[21] and is amenable for the synthesis of diversely functionalized derivatives of **6**.

Besides their potential as synthons, we then evaluated some of the alkynylthiophenes synthesized for in vitro anticancer activity. Selected compounds were tested on a panel of cancer cell lines, for example, HT-29 (colon), NCI-H460 (lung), and LoVo (colon) using the NCI standard protocol for screening anticancer molecules.[22] After treating the cells with compounds at 100 μM concentration initially the percentage growth of cells was measured which is shown in Table 2. Based on the result obtained for compound **3i** against LoVo cell line we tested this compound further at lower concentrations such as 10, 1.0, 0.1, and 0.01 μM against the same cancer cell line (Fig. 2) and the GI_{50} value (the concentration that causes 50% inhibition of cancer cell growth against a cell line is expressed as GI_{50}) for this compound was found to be 47.5 μM. Additionally, the LC_{50} (lethal concentration 50 is the concentration of a compound that kills 50% of cells treated) for **3i** was noted as 100 μM. The

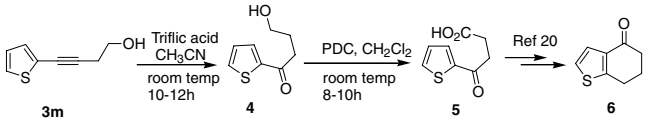
Table 1. Synthesis of alkynylthiophenes in water[a]

Entry	Iodothiophene (**1**)	Alkynes (**2**); R=	Products[b] (**3**)	Yield (%)[c]
1	 **1a**	–$C(CH_3)_2OH$ **2a**	 **3a**	85
2	**1a**	**2a**	**3a**	83
3	**1a**	**2a**	**3a**	87
4	**1a**	–$(CH_2)_3OH$ **2b**	 **3b**	85
5	**1a**	–$CH(OH)CH_3$ **2c**	 **3c**	90
6	**1a**	–$CH_2OC_6H_5$ **2d**	 **3d**	90
7[d]	**1a**	–$CH_2SC_6H_5$ **2e**	 **3e**	86
8[d]	**1a**	–$CH_2NHC_6H_5$ **2f**	 **3f**	88
9	**1a**	–$(CH_2)_5CH_3$ **2g**	 **3g**	87
10	**1a**	–$C_6H_4CH_3$-*p* **2h**	 **3h**	87
11	**1a**	–$CH_2OC_6H_4NO_2$-*p* **2i**	 **3i**	86
12	**1a**	–1-indolyl **2j**	 **3j**	84
13	**1a**	–5-indolyloxy **2k**	 **3k**	85
14[d]	**1a**	–$CH_2OC_6H_4CH_3$-*p* **2l**	 **3l**	85
15[d]	**1a**	–$(CH_2)_2OH$ **2m**	 **3m**	80
16	 **1b**	**2a**	 **3bb**	77
17	 **1c**	**2a**	 **3cc**	78

[a] All the reactions were carried out by using **1** (1.0 equiv), **2** (1.5 equiv), 10% Pd/C (0.026 equiv), PPh_3 (0.20 equiv), CuI (0.05 equiv), and 2-aminoethanol (3 equiv) at 80 °C for 8 h.
[b] Identified by ^1H NMR, IR, and MS.
[c] Isolated yields.
[d] The reaction was carried out for 10h.



Scheme 2.



Scheme 3.

Table 2. In vitro anticancer activities of alkynylthiophenes

Compound	Percentage growth at 100 μM in different cell lines		
	LoVo	H460	HT-29
3a	78	105	95
3d	47	88	63
3i	26	48	44
3h	83	68	83
3bb	78	56	90

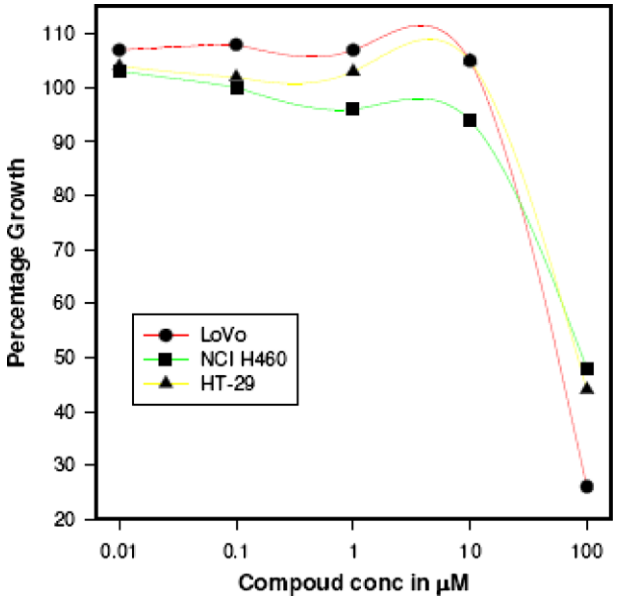


Figure 2. Cell growth inhibition curve of compound **3i**.

present study thus indicates that alkynylthiophene moiety could be a new and potential scaffold for the development of novel anticancer agents.

In conclusion, we have demonstrated that Pd/C-CuI-PPh_3 can be used as an efficient catalyst system for Sonogashira coupling of iodothiophene with terminal alkynes, irrespective of aliphatic or aromatic, in water. The reactions proceed well to afford alkynylthiophenes in good yields. This process is highly reliable and economical and it opens an easy way to access alkynyl heteroarenes of synthetic and potential pharmacological interest. Synthetic application of compound **3m** has been demonstrated. In addition, some of the compounds synthesized showed anticancer properties when tested in vitro against a panel of cell lines.

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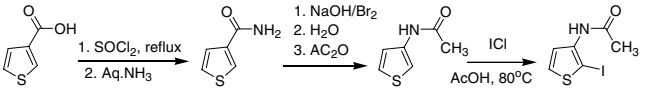
17. In a typical procedure a mixture of 2-iodothiophene (1.42 mmol), 10% Pd/C (0.037 mmol), PPh_3 (0.28 mmol), CuI (0.07 mmol), and ethanolamine (4.16 mmol) in water (10 mL) was stirred at 25–30 °C for 30 min under nitrogen. The acetylinic compound (2.14 mmol) was added, and the mixture was initially stirred at room temperature for 1 h and then at 80 °C for 8–10 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (50 mL), and filterd through Celite. The organic layers collected, washed with water (3× 25 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude residue was purified by column chromatography on silica gel, using light petroleum (60–80 °C)-ethyl acetate to afford the desired product. Spectral data for **3a**: off-white solid; mp 54–55 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.23 (d, J = 5.0 Hz, 1 H), 7.17 (d, J = 4.7 Hz, 1H), 6.93 (m, 1H), 2.05 (br s, –OH), 1.55 (s, 6H); IR (cm^{-1}, $CHCl_3$) 3239.1, 2980.1, 1256.0, 1217.9, 961.6; *m/z* (ES mass) 149 (M^+–OH, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 132.2, 132.0, 127.2, 127.0, 94.7, 76.4, 65.5, 31.5 (2C); UV (nm, MeOH) 360.4, 267.4, 203.4; HPLC 99.3%, column: Zorbax Eclipse XDB C-18 (150 × 4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 12.8 min. Spectral data for **3d**: off-white solid; mp 63–64 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.21 (m, 4H), 6.99–6.93 (m, 4H), 4.91 (s, 2H); IR (cm^{-1}, $CHCl_3$) 2923.3, 2216.2, 1595.8, 1486.3; *m/z* (ES mass) 215 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.7, 132.7 (2C), 129.4 (2C), 127.6, 126.9, 121.4, 114.9 (2C), 87.9, 80.4, 56.6 (CH_2); UV (nm, MeOH) 359.8, 269.2, 202.4; HPLC 99.0%, column: Zorbax Eclipse XDB C-18 (150 × 4.6) mm, mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 17.1 min.
18. The compound **1b** was prepared according to the following Scheme see: (a) Campaigne, E.; Monroe, P. A. *J. Am. Chem. Soc.* **1954**, *76*, 2447; (b) Ishikawa, T.; Mizutani, A.; Miwa, C.; Oku, Y.; Komano, N.; Takami, A.; Watanabe, T. *Heterocycles* **1997**, *45*, 2261.



1b

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21. The 4-keto-4,5,6,7-tetrahydrothianaphthene is a key intermediate for the synthesis of a range of sulfur-containing compounds, see: Mosti, L.; Schenone, P.; Menozzi, G.; Romussi, G. *J. Heterocyl. Chem.* **1982**, *19*, 1057, See also Ref. 19a–b..
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