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Pd/ligand-free synthesis of thienopyranones via Cu-catalyzed coupling-cyclization in PEG 400 under ultrasound

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ABSTRACT

A greener and practical synthesis of 5-substituted thieno[2,3-*c*]pyran-7-ones has been achieved via Cu-catalyzed coupling-cyclization of 3-iodothiophene-2-carboxylic acid with terminal alkynes in the presence of K_2CO_3 in PEG 400 under ultrasound irradiation. A range of thienopyranone derivatives were synthesized by using this inexpensive and Pd- and ligand-free methodology.

Due to the well-known bioisosterism between thiophene and the benzene ring thienopyranones can be considered as alternative scaffolds for isocoumarins[1] in medicinal chemistry and pharmaceutical research. However, unlike isocoumarins as a class of compounds the thienopyranones are rather unusual. Only a few number of thieno[2,3-*c*]pyran-4-ones were synthesized and evaluated for their antileishmanial and antifungal activities.[2] Recently, some of the 5-substituted thieno[2,3-*c*]pyran-7-ones synthesized were tested in vitro for their anticancer activities.[3] Several methods have been reported for the synthesis of thienopyranones[4] including the construction of the pyranone ring on the thiophene moiety either via classical methods or by using Fisher carbene complexes. In our effort[5,6] we have reported the synthesis of 5-substituted thieno[2,3-*c*]pyran-7-ones via 10%Pd/C-CuI-PPh_3 catalyzed coupling-cyclization of 3-iodothiophene-2-carboxylic acid with terminal alkynes in 1,4-dioxane.[3] The methodology however, required the use of two metal catalysts, expensive PPh_3 ligand, and solvent. Very recently, we have developed a greener method for the Cu-mediated synthesis of isocoumarins in the presence of CuI in polyethylene glycol 400 (PEG 400).[7] In further continuation of this work we now report an alternative and environmental friendly synthesis of thienopyranones that is free from the use of any Pd catalysts and ligands. The use of PEG as a solvent in organic reactions is advantageous due to its high boiling, non-hazardous and polar nature thereby allowing its easy recovery (from the reaction mixture) and recyclability. The use of ultrasound in organic reactions[8,9] has also gained considerable attention due to certain advantages over conventional heating. For example, ultrasound irradiation can accelerate chemical reactions, improve yields, shorten reaction times, and enhance selectivity. The present synthesis of thienopyranones therefore involved Cu-catalyzed coupling of 3-iodothiophene-2-carboxylic acid (**1**) with terminal alkynes (**2**) under ultrasound in the presence of K_2CO_3 in PEG 400 (Scheme 1).

In the beginning of our study, the coupling of **1**[3] and 2-methylbut-3-yn-2-ol (**2a**) was used as a model reaction to establish the optimum reaction conditions. Accordingly, the reaction of **1** with **2a** was performed in PEG 400 in the presence of 10 mol % CuI and K_2CO_3 (Table 1, entry 1) when some progress was observed after 24 h of sonication (using SONOREX SUPER RK 510H model producing irradiation of 35 KHz). However, the use of 20 mol % CuI increased the product yield significantly and decreased the reaction time from 24 to 2 h (Table 1, entry 2). A further increase in catalyst quantity did not improve the yield (Table 1, entry 3). To assess the role of ultrasound in the present transformation the reaction of **1** with **2a** was performed in the absence of this irradiation when the formation of **3a** was not observed (Table 1, entry 4). All these reactions were carried out using K_2CO_3 as a base. The use of other bases such as Cs_2CO_3 and K_3PO_4 was also examined

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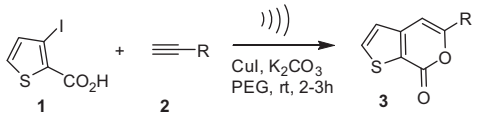
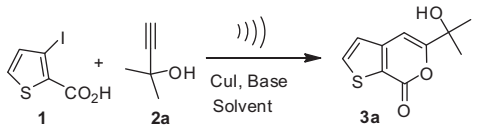


Scheme 1. Cu-mediated synthesis of 5-substituted thieno[2,3-*c*]pyran-7-ones in PEG 400.

Table 1
The optimization of coupling of 3-iodothiophene-2-carboxylic acid (**1**) with 2-methylbut-3-yn-2-ol (**2a**)[a]



Entry	CuI (mol %)	Base	Solvent	Time (h)	Yield[b] (%)
1	10	K_2CO_3	PEG	24	36
2	20	K_2CO_3	PEG	2	77
3	50	K_2CO_3	PEG	2	76
4	20	K_2CO_3	PEG	36	0[c]
5	20	Cs_2CO_3	PEG	4	68
6	20	K_3PO_4	PEG	4	64
7	20	K_2CO_3	EtOH	2	57
8	20	K_2CO_3	*n*-BuOH	2	55

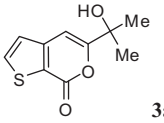
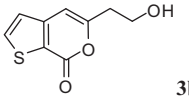
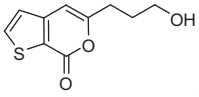
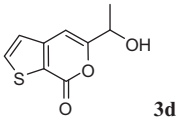
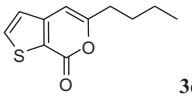
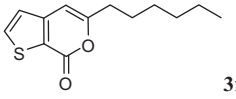
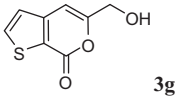
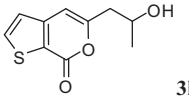
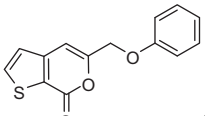
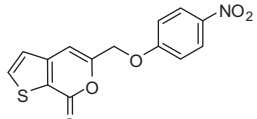
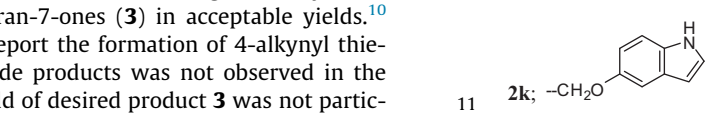
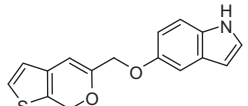
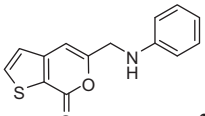
[a] All the reactions were carried out by using 3-iodothiophene-2-carboxylic acid (**1**, 1.0 mmol), 2-methylbut-3-yn-2-ol (**2a**, 1.5 mmol), base (2.0 mmol), and CuI in a solvent (5.0 mL) at room temp (25 °C) in a sonicator under nitrogen.
[b] Isolated yield.
[c] Reaction was carried out in the absence of ultrasound.

and found to be effective (Table 1, entries 5 and 6). The use of other solvents for example EtOH and *n*-BuOH (Table 1, entries 7 and 8) was also investigated. While the reaction proceeded well in these cases the product yield however was inferior compared to PEG 400.

We then decided to expand the scope and generality of this Cu-catalyzed coupling-cyclization in PEG 400 under ultrasound. Thus a range of terminal alkynes (**2**) were reacted with the iodo compound (**1**) under the optimized reaction conditions that is entry 2 of Table 1 and the results are summarized in Table 2. The reaction proceeded smoothly in all these cases affording a variety of 5-substituted thieno[2,3-*c*]pyran-7-ones (**3**) in acceptable yields.[10] Notably, unlike an earlier report the formation of 4-alkynyl thieno[2,3-*c*]pyran-7-ones as side products was not observed in the present case though the yield of desired product **3** was not particularly high. While all these reactions were performed at room temperature a marginal increase of bath temperature (up to ~40 °C) was observed during ultrasound irradiation. Thus the reaction temperature was maintained by adding cold water occasionally. All the compounds synthesized were characterized by NMR, IR, and MS and compared with that reported earlier.[3] The appearance of a signal at the range δ 165–155 ppm in the ^{13}C NMR spectra and IR absorption at 1720–1690 cm^{-1} indicated the presence of a six-membered aromatic lactone ring. Moreover, the C-4 vinylic proton of the lactone ring appeared at ~δ 6.8–6.4.

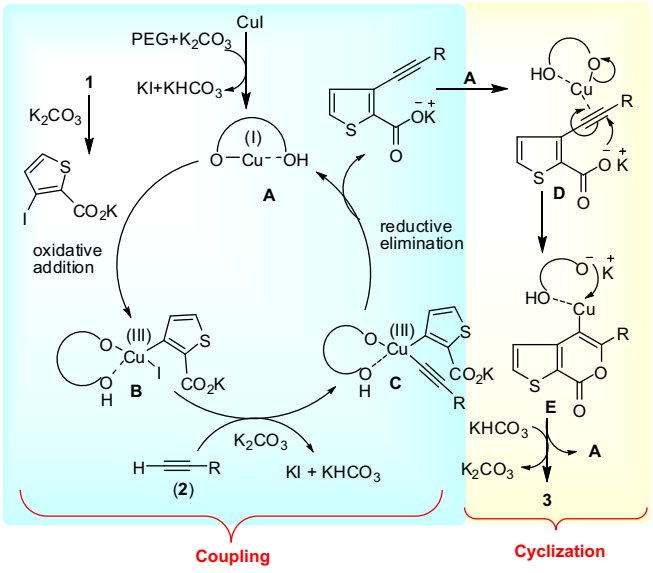
A probable mechanism for the present Cu-catalyzed coupling-cyclization method leading to 5-substituted thieno[2,3-*c*]pyran-7-ones in PEG 400 under ultrasound is shown in Scheme 2. The solvent PEG seems to play the role of a ligand[11] too in the present reaction. Thus, a Cu(I) complex (**A**) formed via the interaction of CuI with PEG[11] under ultrasound, underwent oxidative addition

Table 2
Synthesis of 5-substituted thieno[2,3-*c*]pyran-7-ones via Cu-catalyzed coupling-cyclization in PEG 400 under ultrasound (Scheme 1)[a]

Entry	Alkyne (**2**; R =)	Time (h)	Products (**3**)	% Yield[b]
1	**2a**; $-CMe_2OH$	2	 **3a**	77
2	**2b**; $-CH_2CH_2OH$	2.5	 **3b**	69
3	**2c**; $-CH_2CH_2CH_2OH$	2.5	 **3c**	65
4	**2d**; CHMeOH	2.5	 **3d**	59
5	**2e**; $-CH_2CH_2CH_2Me$	2	 **3e**	63
6	**2f**; $-CH_2(CH_2)_4Me$	2	 **3f**	71
7	**2g**; $-CH_2OH$	3	 **3g**	54
8	**2h**; $-CH_2CHMeOH$	2.5	 **3h**	61
9	**2i**; $-CH_2OPh$	2	 **3i**	79
10	**2j**; $-CH_2OC_6H_4NO_2$-*p*	2	 **3j**	73
11	**2k**; 	2	 **3k**	68
12	**2l**; $-CH_2NHPh$	3	 **3l**	68

[a] All the reactions were carried out by using **1** (1.0 mmol), an appropriate terminal alkyne (**2**, 1.5 mmol), K_2CO_3 (2.0 mmol), and CuI (20 mol %) in PEG (5.0 mL) at room temp (25 °C) in a sonicator under nitrogen.
[b] Isolated yield.

with the carboxylate anion of **1** to afford the arene-Cu species **B**. The reaction of alkyne **2** with **B** in the presence of K_2CO_3 affords the arene-Cu(III)-alkyne species **C**, which on reductive elimination

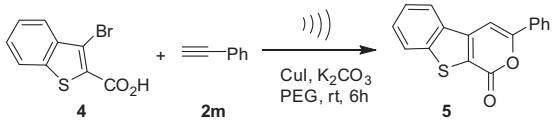


Scheme 2. Proposed mechanism for the Cu-mediated coupling-cyclization of **1** with **2** in PEG under ultrasound.

of 'Cu' furnished the 3-alkynylthiophene-2-carboxylate with the regeneration of catalyst **A**. While it is not clear if ultrasound had an effect on one or more of these individual steps in this pathway the irradiation however played a key role in the overall reaction as is evident from Table 1. It is well known that ultrasound works by the phenomenon of cavitation involving the growth, oscillation, and collapse of bubbles under the action of an acoustic field. Experimental evidences suggest that the cavitational collapse creates drastic conditions inside the medium for an extremely short time (indeed temperature of 2000–5000 K and pressure up to 1800 atmosphere have been produced inside the collapsing cavity under sonic conditions).[8a,12] This collapse also causes strong physical effects such as shear forces, jets, and shock waves outside the bubble. As a result of these cavitation-induced overall effects the chemical transformations are driven with remarkable efficiency and speed when performed under ultrasound. This is probably the reason for the success of present coupling-cyclization reaction in PEG under ultrasound in the absence of which the reaction did not proceed.

To expand the scope and generality of the present methodology further we examined the coupling of 3-bromobenzo[*b*]thiophene-2-carboxylic acid[13] (**4**) with phenyl acetylene (**2m**) in the presence of CuI and K_2CO_3 in PEG 400 at room temp (25 °C) in a sonicator under nitrogen (Scheme 3). While the reaction proceeded under this condition affording the expected product that is 3-(phenyl)benzothieno[2,3-*c*]pyran-1-one[14] (**5**) in 43% yield the duration of the reaction was much longer (6 h) and a substantial quantity of 1,4-diphenylbuta-1,3-diyne (as a result of dimerization of alkyne **2m**) was isolated as a side product in this case.

We have developed an alternative and convenient protocol for the synthesis of 5-substituted thieno[2,3-*c*]pyran-7-ones. Some of these compounds were already tested for their growth inhibition



Scheme 3. Cu-mediated coupling of 3-bromobenzo[*b*]thiophene-2-carboxylic acid (**4**) with phenyl acetylene (**5m**) in PEG 400 under ultrasound.

potential against a panel of cancer cell lines e.g. HT-29 (colon), NCI-H460 (lung), and LoVo (colon) in vitro.[3] The compounds **3a** and **3i** have shown encouraging activities though their mechanism of pharmacological action was not clearly understood. Being bioisosteric analogues of isocoumarins[15] these compounds may also behave as inhibitors of the urokinase-type plasminogen activator (uPA). The uPA has been considered as a promising molecular target for the development of small molecule based anticancer agents as its elevated expression is associated with tumor cell growth, migration, and angiogenesis. The role of isocoumarin framework in binding with uPA has been investigated in 3D-QSAR studies employing linear and non-linear regression analysis methods.[16] Apart from the key role of the pyranone ring the study suggested considerable influences of the benzene ring of the isocoumarin framework toward uPA inhibition. The electron rich thiophene moiety of **3** therefore may play an interesting role in the potential inhibition of uPA. Thus, the present class of thienopyranones is of further interest and deserves continued pharmacological investigations.

In conclusion, Cu-catalyzed coupling-cyclization of 3-iodothiophene-2-carboxylic acid with terminal alkynes in the presence of K_2CO_3 in PEG 400 under ultrasound irradiation afforded an inexpensive and easy access to 5-substituted thieno[2,3-*c*]pyran-7-ones. The methodology is free from the use of hazardous catalysts, reagents, or solvents. A number of thienopyranone derivatives were synthesized by using this Pd- and ligand-free methodology. A proposed reaction mechanism and the possible mode of pharamacological action of this class of compounds are presented. Overall, the methodology being amenable for the construction of diversity based library of small molecules related thienopyranone framework may find wide application in organic synthesis/medicinal chemistry.

Acknowledgments

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10. *General method for the synthesis of 5-substituted thieno[2,3-c]pyran-7-ones (**3**):* a mixture of 3-iodo thiophene-2-carboxylic acid (**1**, 1.0 mmol), an appropriate terminal alkyne (**2**, 1.0 mmol), CuI (20 mol %) and K_2CO_3 (2.0 mmol) in PEG (5.0 mL) was sonicated at 25–30 °C for the time indicated in Table 2 (the progress of the reaction was monitored by TLC). After completion of the reaction, the mixture was diluted with EtOAc (20 mL) and filtered through celite. The filtrate was collected and washed with water (20 mL). The EtOAc layer was collected, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel using EtOAc–petroleum ether. Spectral data of selected compounds; compound **3a**: white solid, mp 86–87 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.81 (d, J = 5.3 Hz, 1H), 7.16 (d, J = 5.0 Hz, 1H), 6.8 (s, 1H, CH=C), 2.25 (br s, –OH), 1.60 (s, 6H, CH_3); IR (cm^{-1}, KBr) 3495, 1734 (C=O); m/z (ES Mass) 211 (M$^+$,100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.6 (C=O), 155.5, 147.4, 136.6, 124.5(2C), 97.2, 71.1, 28.2 (2C,

CH_3); compound **3b**: low melting solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 5.0 Hz, 1H), 7.13 (d, J = 5.3 Hz, 1H), 6.57 (s, 1H), 4.02 (t, J = 6.0 Hz, 2H), 2.83 (t, J = 6.0 Hz, 2H), 1.63 (br s, –OH); IR (cm^{-1}, $CHCl_3$) 3435, 1716 (C=O); m/z (ES Mass) 197 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.5 (C=O), 152.1, 147.3, 136.5, 124.1 (2C), 102.3, 59.5 (CH_2), 29.5 (CH_2).

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13. (a) Cross, P. E.; Dickson, R. P.; Parry, J. M.; Randal, J. M. *J. Med. Chem.* **1989**, *29*, 1643; (b) *Preparation of 3-bromobenzo[b]thiophene-2-carboxylic acid* (**4**)*:* To a solution of commercially available benzo[*b*]thiophene-2-carboxylic acid (1 g, 5.61 mmol) and anhydrous NaOAc (1.0 g, 12.1 mmol) in glacial acetic acid (30 mL) was added bromine (2.48 g, 31.4 mmol) drop wise and slowly. The reaction mixture was stirred at 55–60 °C under nitrogen for 24 h. The mixture was poured into ice water (170 mL). The resulting precipitate was filtered, washed with cold water, (3 × 30 mL) and then EtOH (20 mL) and dried. The solid obtained was recrystallized from hot acetone to give the desired product as a colorless solid (yield 50%); mp 279–281 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.03–7.98 (m, 2H), 7.66–7.57 (m, 2H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 161.8 (C=O), 139.3, 138.6, 128.3, 125.7, 125.5, 122.7, 115.1; m/z (ES Mass) 257 (M+1, 100%).
14. *3-(Phenyl)benzothieno[2,3-c]pyran-1-one* (**5**)*:* white solid (crystallized from ether/petroleum ether); mp 211–213 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11–8.09 (m, 1H, ArH), 7.98–7.93 (m, 3H, ArH), 7.64–7.46 (m, 5H, ArH), 7.39 (s, 1H, 4-CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.8 (C=O), 157.4, 143.7, 143.6, 134.2, 131.7, 130.3, 129.2, 128.9 (2C), 125.4 (2C), 125.4, 123.6, 123.6, 122.5, 96.9 (4-CH); m/z (ES Mass) 278 (M^+, 100%).
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