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New One Pot and Efficient Four-Components Reaction for Synthesis of 2,3-Dihydrothiophene Carbamate Derivatives

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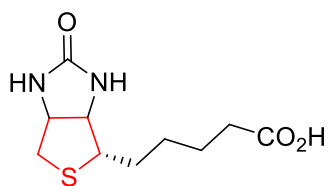
A new series of 2,3-dihydrothiophenes bearing ethyl carbamate moiety (**4a-4l**) was designed and synthesized through a facile synthetic route involving domino ring-opening/recyclization reaction of 1,3-thiazolidinedione. The synthesis was achieved via a novel one-pot four-component reaction of aromatic aldehydes, malononitrile and 1,3-thiazolidinedione, using 4-dimethylaminopyridine as base catalyst under ethanol reflux. The molecular

structures of the synthesized compounds were elucidated by usual spectroscopic techniques such as FT-IR, ¹H NMR, ¹³C NMR and HRMS methods. X-ray diffraction was used to confirm the structures of compounds **4d** and **4j**. Readily available starting materials, atom-efficient routes employing more mild reaction conditions and environmentally benign are the attracting features of this current protocol.

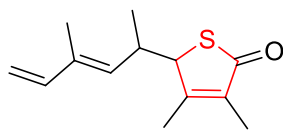
Introduction

Consisting of natural and synthetic products, heterocycles constitute the largest part of organic molecules. Endowed with multiple biological and pharmacological properties, they are of considerable interest to industry, medicine and the daily life of mankind.^[1] Among these compounds, we can cite the sulfur-containing heterocycles

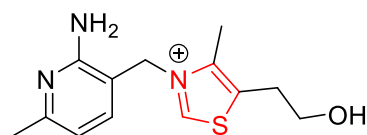
which are present in the structure of many natural substances such as biotin, thiolactomycine or thiamine (**Figure 1**), as well as in pharmaceutical products currently used as an anticoagulant, antipsychotic, antidepressant and antibiotic in the treatment of some diseases (**Figure 2**).^[2]



Biotine
(vitamin B8)

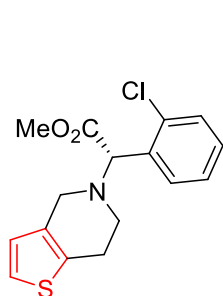


Thiolactomycine
(antibiotic)

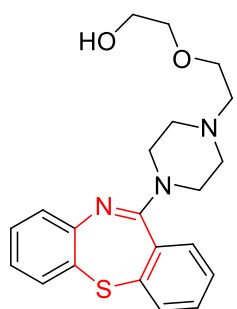


Thiamine
(vitamin B1)

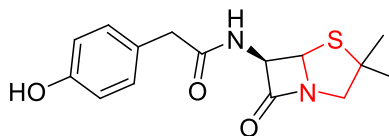
Figure 1: Some sulfur-containing natural heterocycles



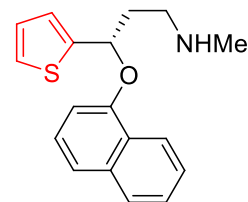
Plavix
(anticoagulant)



Seroquel
(antipsychotic)



Amoxicilline
(antibiotic)



Cymbalta
(antidepressant)

Figure 2: Some sulfur-containing heterocycles with biological activities

A special class of these sulfur-containing heterocyclic compounds is that which has the 2,3-dihydrothiophene ring, sometimes referred to as 2-thiole. This nucleus is widely present in many natural or synthetic

products which exhibit important medicinal and biological activities. They can be antibacterial, antifungal, anticancer, anti-inflammatory and anti-HIV (Figure 3).^[3-10]

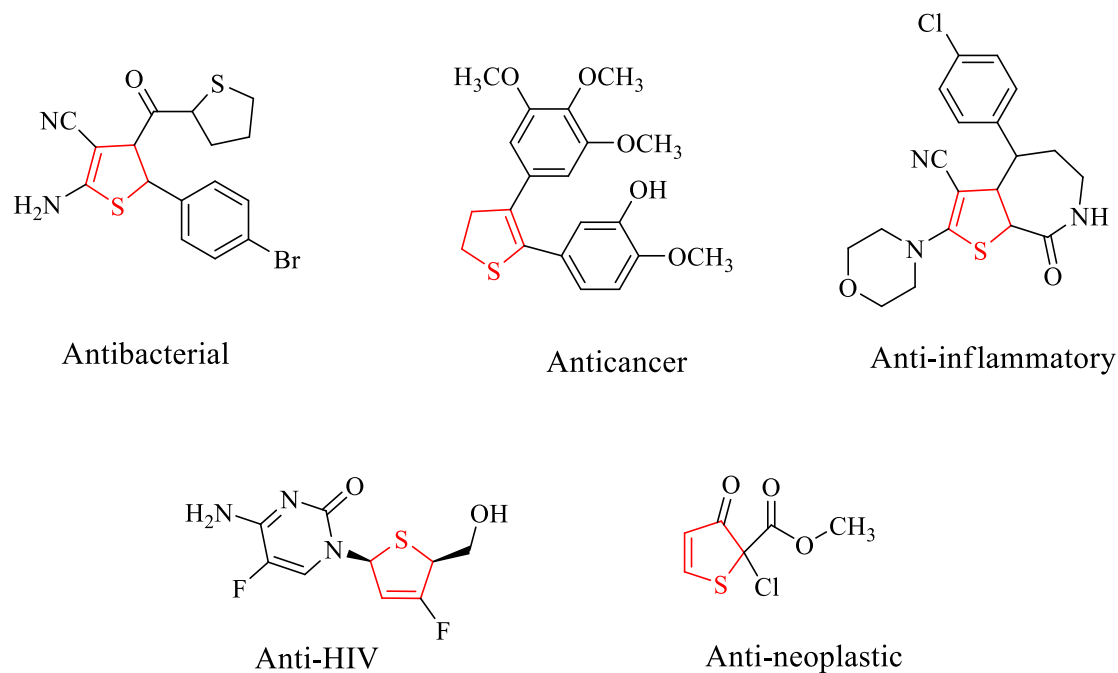


Figure 3: Some 2,3-dihydrothiophene derivatives with biological activities

2,3-dihydrothiophene derivatives are also good intermediates in the synthesis of a variety of molecules which exhibit interesting biological and pharmacological activities such as thiophenes, thionucleosides and penicillin analogues.^[10-16]

Given their importance, several multi-step synthesis methods of 2,3-dihydrothiophene derivatives are described for the preparation of target molecules which exhibit biological and pharmacological activities.^[17-35]

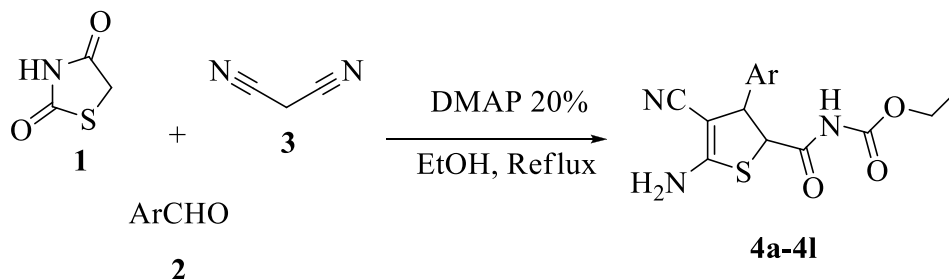
Multicomponent reactions represent a remarkable strategy for quickly and directly accessing complex molecules from simple precursors. These reactions offer multiple advantages such as economy of atoms and steps, reduction of waste and reduction of synthesis time. Only a few multicomponent methods have been disclosed for the construction of dihydrothiophene derivatives. All of these methods consist of a four-component reaction between aromatic aldehydes, malonitrile, 2,3-

thiazolidinedione and amino derivatives such as α -aminoesters, primary and secondary aliphatic or cyclic amines, in the presence of a variety of catalysts and under different conditions.^[14, 36-45]

It has been described that a mixture of arylidenemalononitrile and 1,3-thiazolidinedione brought to reflux in ethanol in the presence of piperidine leads to pyrano [2,3-d][1,3]thiazole derivatives with good yields.^[46-47] Given that arylidenemalonitrile can be easily formed *in situ*, via the condensation of Knoevenogel between an aromatic aldehyde with malonitrile, and in the continuation of our research of new methods of synthesis in heterocyclic series, we set out to study the three-component reaction between an aromatic aldehyde, malonitrile and 1,3-thiazolidinedione, refluxed in ethanol, in the presence of N,N-dimethylaminopyridine, as a catalyst. Here we report the unexpected results we have arrived at. In fact we don't get the expected

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pyrano[2,3-*d*][1,3]thiazoles but we get a new series of 2,3-dihydrothiophene carbamates (**Scheme 1**).



Scheme 1: Synthesis of 2,3-dihydrothiophene carbamate derivatives (4a-4l)

This unexpected result is important to us not only because we believe to establish a new one-pot four-component domino reaction, but also because of the biological interest of 2,3-dihydrothiophene derivatives while all

the described preparation procedures of dihydrothiophenes and the like have suffered from synthetic restriction to only a limited range of dihydrothiophene ureidoformamides.^[14, 36-45]

Results and discussion

To carry out our study, we chose as a model a mixture of *o*-methoxybenzaldehyde, malononitrile and 1,3-thiazolidinedione that we subjected to different operating conditions. In a first test, the model mixture was refluxed in ethanol for 4 hours in the presence of sodium carbonate. After treatment and purification, all the analytical data of the product obtained showed the introduction of the ethanol unit into its structure. So it was not the expected pyrano [3,2-*d*]-5,7-thiazole but a new 2,3-dihydrothiophene substituted with the ethyl carbamate moiety which was produced in a

yield of 30 %. Another unexpected discovery occurred when we obtained 5-arylideneethiazlidinedione as a by-product. In this protocol, ethanol behaves both as a solvent and as a nucleophile, was a reagent needed to initiate the opening process of the 1,3-thiazolidinedione ring. Encouraged by this positive result, which constitutes a new four-component synthesis route for dihydrothiophene carbamates, we subjected our three starting reagents to various operating conditions. The results obtained are summarized in Table 1.

Table 1. A comparative study of efficiency of various catalysts for the synthesis of ethyl (5-amino-4-cyano-3-(2-methoxyphenyl)-2,3-dihydrothiophene-2-carbonyl) carbamate (**4a**)

Entry	Catalyst (mmol)	Representative molar ratio of reactants 1 , 2 and 3	Medium	Time (h)	Temperature (°C)	Yield (%) ^[a]
1	Na ₂ CO ₃ (0.2)	(1 : 1 : 1)	EtOH	4	reflux	30
2	K ₂ CO ₃ (0.2)	(1 : 1 : 1)	EtOH/H ₂ O	4	reflux	18
3	K ₂ CO ₃ (0.2)	(1 : 1 : 1)	EtOH	4	room temp.	trace
4	DMAP (0.2)	(1 : 1 : 1)	EtOH	4	reflux	34
5	Et ₃ N (0.2)	(1 : 1 : 1)	EtOH	4	reflux	15
6	Ph ₃ P (0.2)	(1 : 1 : 1)	EtOH	4	reflux	-
7	Ba(OH) ₂ (0.2)	(1 : 1 : 1)	EtOH	4	reflux	trace
8	C ₆ H ₅ B(OH) ₂ (0.2)	(1 : 1 : 1)	EtOH	4	reflux	-
9	H ₃ BO ₃ (0.2)	(1 : 1 : 1)	EtOH	4	reflux	-
10	NH ₂ SO ₃ H (0.2)	(1 : 1 : 1)	EtOH	4	reflux	-
11	C ₁₂ H ₁₃ NO ₃ S (0.2)	(1 : 1 : 1)	EtOH	4	reflux	-
12	-	(1 : 1 : 1)	EtOH	4	reflux	-
13	DMAP (0.1)	(1 : 1 : 1)	EtOH	4	reflux	25
14	DMAP (0.3)	(1 : 1 : 1)	EtOH	4	reflux	18
15	DMAP (0.2)	(1 : 1.2 : 3)	EtOH	4	reflux	39
16	DMAP (0.2)	(1 : 1.2 : 5)	EtOH	4	reflux	52
17	DMAP (0.2)	(1 : 1.2 : 7)	EtOH	4	reflux	37

[a] Isolated pure products.

First, to find a reaction medium suitable for the synthesis of the title compounds, the model reaction of *o*-methoxybenzaldehyde, malononitrile and 1,3-thiazolidinedione was carried out in EtOH, and in an EtOH / H₂O mixture. As emerges from Table 1, the best results were obtained in ethanol as the reaction medium. Then, the effect of the reaction temperature and the amount of catalyst was also carried out.

Besides, to improve the reaction speed as well as the yield, we performed the same four-component domino reaction at reflux of ethanol, using various catalysts such as phenylboronic acid, boronic acid, acid sulfamide, potassium carbonate, triethylamine and pyridinium *p*-toluenesulfonate. Examination of Table 1, entry 16, shows that the best expected

product yield (52%) was obtained in ethanol at reflux, and 4-dimethylaminopyridine as a 20 mol% catalyst. Further increase in the amount of catalyst did not have a positive effect on the yield (Table 1, entries 12-14). On the other hand, increasing the amount of malononitrile to 5 equivalents (Table 1, entry 16) leads to a better yield, while an increase in the amount of malononitrile to more than 5 equivalents has shown no improvement in the yield.

Accordingly, the optimum conditions for the four-component synthesis of the ethyl 5-Amino-4-cyano-3-(2-methoxyphenyl)-2,3-dihydrothiophene-2-carbonyl) carbamate are 1 equivalent of *o*-methoxybenzaldehyde, 1 equivalent of thiazolidinedione, 5 equivalents of malononitrile and 20 mol% of 4-

1 dimethylaminopyridine relative to the
2 aldehyde, at reflux in ethanol.

3 In a second step, the optimal conditions
4 previously chosen are applied to a series of
5 differently substituted aromatic aldehydes.
6 The results are collated in Table 2 which
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show that the desired products are obtained
with average to good yields which vary
between 40 and 70% (entries 2 and 10).

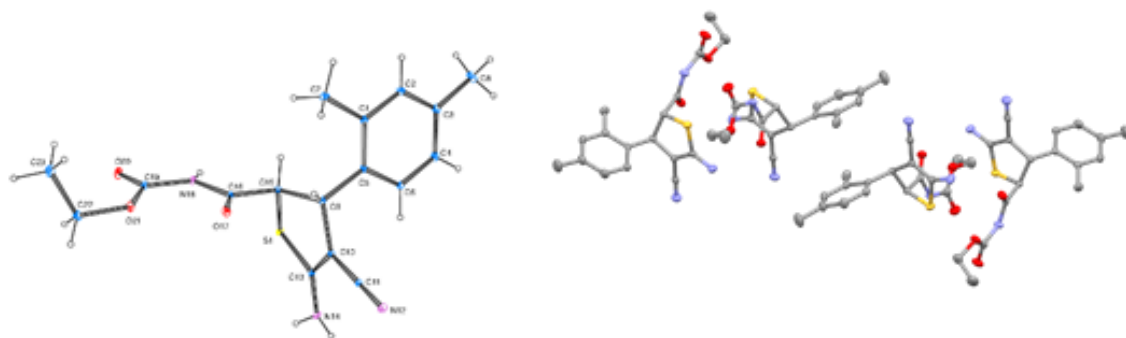
10 **Table 2.** Synthesis of ethyl (5-amino-4-cyano-3-aryl-2,3-dihydrothiophene-2-carbonyl)
11 carbamate derivatives under optimized reaction conditions.
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13 Entry	14 Ar	15 Compound	16 Time (h)	17 Yield (%) ^[a]	18 M.p. (°C) 19 Measured
20 1	21 2-CH ₃ O-C ₆ H ₄	22 4a	23 4	24 52	25 216-218
26 2	27 3-CH ₃ -C ₆ H ₄	28 4b	29 4	30 40	31 194-196
32 3	33 4-C ₂ H ₅ -C ₆ H ₄	34 4c	35 4	36 42	37 175-177
38 4	39 2,4-(CH ₃) ₂ -C ₆ H ₃	40 4d	41 4	42 45	43 208-210
44 5	45 2,5-(CH ₃) ₂ -C ₆ H ₃	46 4e	47 4	48 43	49 201-203
50 6	51 3,4,5-(CH ₃ O) ₃ -C ₆ H ₂	52 4f	53 4	54 47	55 180-182
56 7	57 3-Br-4-OCH ₃ -C ₆ H ₃	58 4g	59 4	60 55	61 225-226
62 8	63 4-Br-C ₆ H ₄	64 4h	65 3	66 43	67 215-217
68 9	69 4-Cl-C ₆ H ₄	70 4i	71 3	72 48	73 206-208
74 10	75 2,4-Cl ₂ -C ₆ H ₃	76 4j	77 3	78 70	79 246-248
80 11	81 2-NO ₂ -5-Cl-C ₆ H ₃	82 4k	83 3	84 68	85 200-202
86 12	87 3-NO ₂ -4-Cl-C ₆ H ₃	88 4l	89 3	90 61	91 211-212

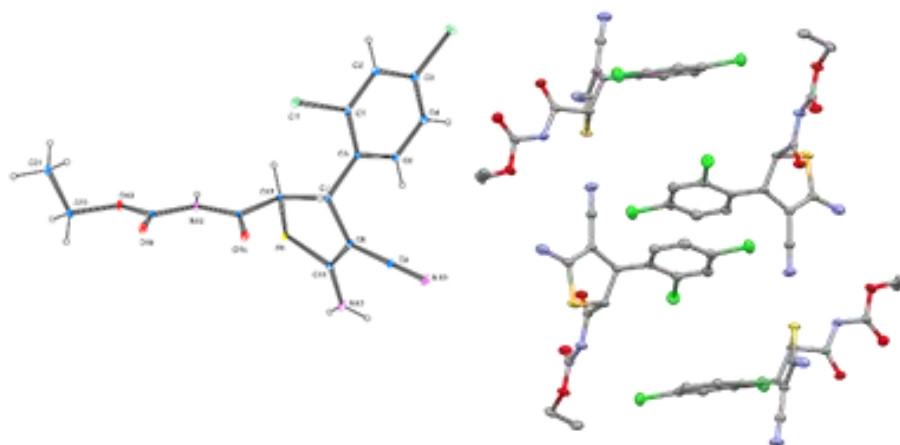
92 [a] Isolated pure product.

93 All structures were elucidated by ¹H NMR,
94 ¹³C NMR, high resolution mass
95 spectroscopy and are consistent with the
96 proposed structures. In particular, ¹H NMR
97 and ¹³C NMR show the existence of the
98 signals of the ethyl group. In addition, the

structures of compound **4d** and **4j** were also
checked and confirmed by X-ray diffraction
(**Figures 4 and 5**).^[48]



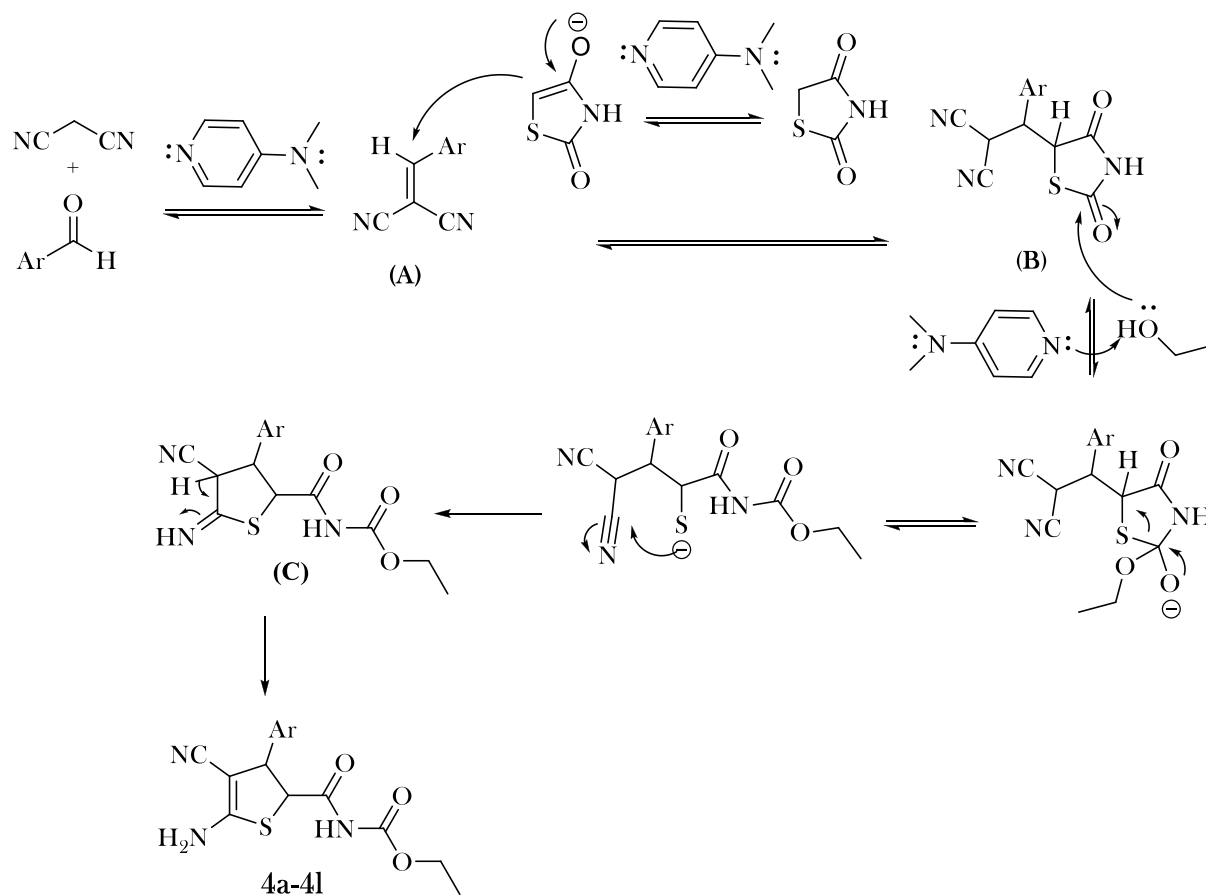
14 **Figure 4: ORTEP and tacking of the structure of compound 4d**



38 **Figure 5: ORTEP and tacking of the structure of compound 4j**

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42 A possible reaction mechanism is suggested
43 to explain this novel domino four-
44 component reaction of aryl aldehydes,
45 malononitrile, 1,3-thiazolidinedione and the
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formation of 2,3-dihydrothiophenes (**4a–4l**)
in the presence of DMAP at ethanol reflux,
which is is illustrated in **Scheme 2**.



Scheme 2: Suggested mechanism of the formation of 2,3-dihydrothiophenes (4a-4l)

First, DMAP catalyzed the formation of arylidenemalononitrile obtained from the Knoevenagel condensation of aromatic aldehyde with malononitrile after removing a water molecule (intermediate A). In the next step, with the presence of DMAP, 1,3-thiazolidinedione transforms into its corresponding enolate and is added to arylidenemalononitrile by addition of Michael to give an intermediate containing 1,3-thiazolidinedione (intermediate B). Then, the nucleophilic addition of the ethanol unit at the C-2 carbonyl group of the thiazolidinedione moiety of (B) triggers the pivotal ring-opening reaction.

At this stage, and in line with the Sun's hypothesis^[36] the resulting sulfide anion intercepts the tethered cyano group providing, after protonation, the sulfur containing five-membered ring intermediate (C). Eventually, the 2,3-dihydrothiophene derivatives 4 are formed following imine-enamine tautomerization process.

The presence of DMAP as a base makes ethanol more nucleophilic by the polarization of the O-H bond and facilitates the attack of the thiazolidinedione nucleus.

Conclusion

In this work, we have developed for the first time a new way for the synthesis of 2,3-dihydrothiophene carbamate derivatives by a four-component reaction and resulting from an opening and rearrangement of the 1,3-thiazolidinedione ring under the action of ethanol. Furthermore, this reaction demonstrates a wide tolerance to the functional groups and opens the way to the synthesis of new heterocyclic analogues with greater structural diversity. The present methodology offers advantages such as simple reaction conditions, reduced reaction times, acceptable yields, the absence of hazardous organic solvents or the formation of side products. In addition, like all multi-component reactions, there is a saving of energy, atoms and time: this is an environmentally friendly method.

Cristallographica Data

The complete crystallographic data for compounds **4d** and **4j** have been deposited with Cambridge Cristallographic Data as CCDC 2115942 and CCDC 2115943 respectively and can be obtained from Cambridge Cristallographic Data via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information Summary

The experimental details including synthetic method, spectral data, copies of

¹H and ¹³C NMR spectra are given in the electronic supporting information.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest

Keywords : 2,3-Dihydrothiophene, 4-Dimethylaminopyridine, Ethyl Carbamate, Four-Component Reaction, 1,3-Thiazolidinedione

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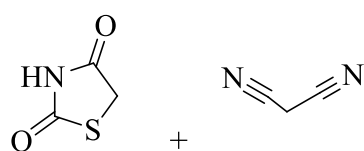
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contain the supplementary crystallographic data
of **4j** and **4d** can be obtained from Cambridge
Cristallographic Data via
www.ccdc.cam.ac.uk/data_request/cif.

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11
12
13
14 Table of Contents entry
15
16
17
18
19
20



27 ArCHO

28 DMAP
29 EtOH
30 Reflux

