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Assembly of Fully Substituted 2,5-Dihydrothiophenes via a Novel Sequential Multicomponent Reaction

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A new and efficient synthesis of fully substituted 2,5-dihydrothiophenes by a sequential one-pot four component reaction between primary amines, β-ketoesters, aryl isothiocyanates and 1,2-diaza-1,3-dienes (DDs) is reported. A careful selection of the starting materials enables the choice up to six different variations in the architecture of the final products. Furthermore, the acidic treatment of the so obtained 2,5-dihydrothiophenes furnishes the corresponding 5-amino thiophene-2,4-dicarboxylates.

Introduction

One of the main aim for synthetic chemists is the development of highly efficient procedures to assemble valuable compounds with high structural complexity resorting to simple available materials.[1] This request can be meet by exploiting the multicomponent reactions (MCRs) that allow incorporation of three or more reactants into the final products. MCRs lead to wide molecular diversity, minimizing the work-up procedures and consequently saving both time and solvents.[2] A class of MCRs is represented by the sequential reactions, where the reagents are added consecutively in a defined order in the same reaction environment under constant conditions. In this way, it is possible to stop the synthetic sequence at every step, and the intermediates can be isolated.[3]

Thiophene is the key structural unit of numerous pharmacophores such as Plavix, (adenosine diphosphate $P2Y_{12}$ receptor antagonist),[4] Raloxifene (selective estrogen receptor modulator),[5] PaTrin 2 (MGMT inactivating drug),[6] articaine (local anaesthetic),[7] Cymbalta (selective serotonin norepinephrine reuptake inhibitor).[8] Furthermore, its peculiar electronic properties and the relevant structural rigidity make the thiophene derivatives interesting cores in the production of innovative organic materials like organic semiconductors, organic light emitting diodes (OLED), organic photovoltaic (OPV), organic field effect transistors (OFET), solar cells, liquid crystals.[9]

About the preparation of thiophenes, a plethora of synthetic approaches has been reported, some of which can be related to classical Gewald, Fiesselmann, Paal-Knorr, and Hinsberg reactions,[10] and many other examples.[11] However, most of these procedures require multistep protocols with consequent laborious isolation operations.

Also the dihydrothiophene compounds represent a common structural motif of numerous bioactive derivatives and they have shown to be versatile intermediates for synthetic applications.[12] Consequently, notable attention has been directed toward new and convenient synthetic procedures to prepare both dihydrothiophenes and thiophenes.

In continuation of our studies on exploring the versatility of 1,2-diaza-1,3-dienes (DDs) in heterocyclic ring assemblies,[13,14] and inspired by the intriguing work of Alizadeh,[15a] we herein report the results of the reaction between DDs and 3-alkylamino-2-(carbamothioyl)but-2-enoates (ACTs)[15] that furnishes fully substituted 2,5-dihydrothiophenes.

Results and discussion

In order to realize a one-pot reaction by sequential addition of the reagents, we began our investigations on the preparation of ACTs **5** (Table 1). The described methodology requires the preliminary formation of enamino ester intermediates,[16] that in turn react with isothiocyanates to produce the desired ACTs **5**. Among all the proposed procedures,[15] Alizadeh describes the most convenient way performed under solvent free conditions (SFC).[15a]

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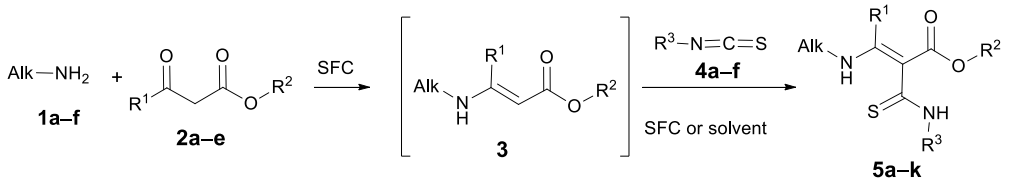
However, Alizadeh didn't isolate directly the ACT derivatives as he reported the one-pot synthesis of the final thiazepine derivatives. In order to optimize the conditions for the ACT preparation, initially the *n*-butyl amine **1a**, the ethyl acetoacetate **2a** and the phenyl isothiocyanate **4a** were chosen as representative model (Table 1, entries 1–9). At the outset, one equivalent of amine **1a** (0.5 mmol) was added in SFC to the β-ketoester **2b** (0.5 mmol) at room temperature. After 0.5 h the enamino ester intermediate **3** was quantitatively formed (TLC analysis), so phenyl isothiocyanate **4a** was added directly to the reaction medium. After 10.0 h the intermediate **3** was completely converted in the corresponding ethyl 3-(butylamino)-2-(phenylcarbamothioyl)but-2-enoate **5a** (Table 1, entry 1). Under these conditions also the 1-butyl-3-phenylthiourea as by-product was formed. So, a slight excess of β-ketoester **2a** (0.55 mmol) was added to completely convert the amine **1**, and to prevent its nitrogen nucleophilic attack to the isothiocyanate **4a** leading to the unwanted thiourea (Table 1, entry 2). In this latter case, only traces of thiourea were detected and ACT **5a** was obtained in 70% yield. No improvement was found employing a larger excess of **2a** (Table 1, entry 3). An increment of the temperature does not influence the reaction (Table 1, entry 4). The addition of the phenyl isothiocyanate **4a** to the enamino ester **3** makes the reaction medium very viscous, and also under vigorous magnetically stirring the homogeneity of the mixture is not optimal. To overcome this drawback, various solvents were added with the phenyl isothiocyanate to the enamino ester formed under SFC (Table 1, entries 5–9). Methanol resulted the optimal solvent for this reaction both in terms of yields and in consideration of the spontaneous precipitation of the pure ACT **5a** under these conditions (Table 1, entry 9). At this juncture, a series different primary alkylamines were tested (Table 1, entries 10–14). The steric hindrance has a decisive impact on efficiency of the process: the best results were obtained using *n*-butyl amine, while in the case of *tert*-butyl amine, only the corresponding thiourea was collected (Table 1, entry 14). With these optimized conditions, some ACTs **5a–k** were synthesized to verify the influence of the different substituents on the β-ketoesters and on the isothiocyanates. Different β-ketoesters **2a–e** were employed with success, and only low variations on the yields were observed.[16,17]

Table 1: Synthesis of 3-alkylamino-2-(carbamothioyl)but-2-enoates **5a–k**.



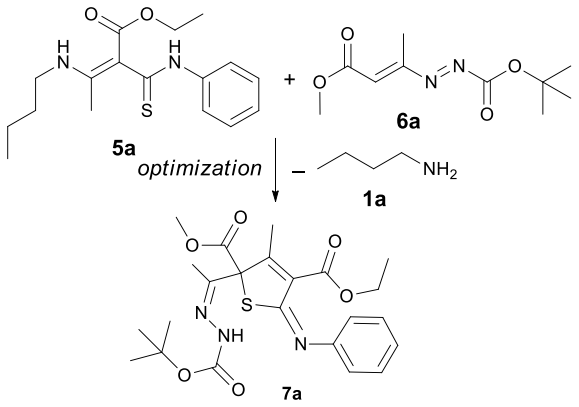
Entries	1	Alk	2	R^1	R^2	4	R^3	5	Solvent	Yield (%)[a,b]
1[c]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC	58[d]
2[e]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC	70[f]
3[g]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC	68[f]
4[e,h]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC	70[f]
5[e,i]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC/ACN	63[f]
6[e,i]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC/THF	61[f]
7[e,i]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC/DCM	58[f]
8[e,i]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC/EtOH	76[f]
9[e,h]	**1a**	*n*-Bu	**2a**	Me	Et	**4a**	Ph	**5a**	SFC/MeOH	78[f]
10[e,i]	**1b**	Bn	**2a**	Me	Et	**4a**	Ph	**5b**	SFC/MeOH	54
11[e,i]	**1c**	$PhCH_2CH_2$	**2a**	Me	Et	**4a**	Ph	**5c**	SFC/MeOH	53
12[e,i]	**1d**	$CH_3CH_2CH(CH_3)$	**2a**	Me	Et	**4a**	Ph	**5d**	SFC/MeOH	34
13[e,i]	**1e**	$(CH_3)_2CHCH_2$	**2a**	Me	Et	**4a**	Ph	**5e**	SFC/MeOH	60[f]
14[e,i]	**1f**	*t*-Bu	**2a**	Me	Et	**4a**	Ph	-	SFC/MeOH	-[j]
15[e,i]	**1a**	*n*-Bu	**2b**	Me	Me	**4a**	Ph	**5f**	SFC/MeOH	82[f]
16[e,i]	**1a**	*n*-Bu	**2b**	Me	Me	**4b**	*p*-MeOPh	**5g**	SFC/MeOH	77[f]
17[e,i]	**1a**	*n*-Bu	**2a**	Me	Et	**4c**	*p*-ClPh	**5h**	SFC/MeOH	75[f]
18[e,i]	**1a**	*n*-Bu	**2b**	Me	Me	**4d**	*p*-NO_2Ph	-	SFC/MeOH	-[k]
19[e,i]	**1a**	*n*-Bu	**2b**	Me	Me	**4f**	CO_2Et	-	SFC/MeOH	-[k]
20[e,i]	**1a**	*n*-Bu	**2c**	Me	Bn	**4e**	Me	**5i**	SFC/MeOH	13
21[e,i]	**1a**	*n*-Bu	**2d**	Et	Me	**4c**	*p*-ClPh	**5j**	SFC/MeOH	66[f]
22[e,i]	**1a**	*n*-Bu	**2e**	*n*-Pr	Et	**4a**	Ph	**5k**	SFC/MeOH	57[f]

*[a]Yields of isolated ACT **5** based on alkylamines **1**. [b]Reaction conditions: alkylamines **1** (0.5 mmol) were added to β-ketoesters **2a–e** under solvent-free conditions at room temperature. After 0.5 h aryl isothiocyanates **4a–f** (0.5 mmol) were added and the reactions were stirred until the disappearance of the enamino esters **3** (monitored by TLC). [c]0.50 mmol of β-ketoesters **2a–e** were added. [d]1-Butyl-3-phenylthiourea as by-product was isolated in 22% yield. [e]0.55 mmol of β-ketoesters **2a–e** were added. [f]Only trace of 1-butyl-3-phenylthiourea was detected. [g]0.65 mmol of β-ketoester **2b** were added. [h]Reaction conducted at 50 °C. [i]Aryl*

*isothiocyanates **4a–f** (0.5 mmol) were added to the reaction medium in 1.5 mL of the indicated solvent. [j]Only 1-tert-butyl-3-phenylthiourea was formed. [k]Complicated reaction mixture.*

Instead, the substituent (R^3) on isothiocyanates **4** considerably affects the reaction outcome. In fact, only phenyl- and aryl-isothiocyanates **4a–c** bearing an electron-donator group such as the methoxy moiety or a weakly electron-withdrawing group as the chlorine furnish the corresponding ACTs in appreciable yields; on the other hand, *p*-nitrophenyl- or ethoxycarbonyl-isothiocyanate **4d,f** unfortunately led to complicated mixture of products in which only traces of the corresponding ACTs are present, visible to the naked eye thanks to the typical yellow colour of these compounds. In the case of the methyl isothiocyanates **4e**, the corresponding ACT **5i** was obtained in low yield. Thus, a preliminary study of the next step of this sequential reaction was conducted using DD **6a** and ACT **5a** chosen as examples (Table 2).

Table 2: Screening of different conditions in the reaction between **DD 6a** and **ACT 5a**.



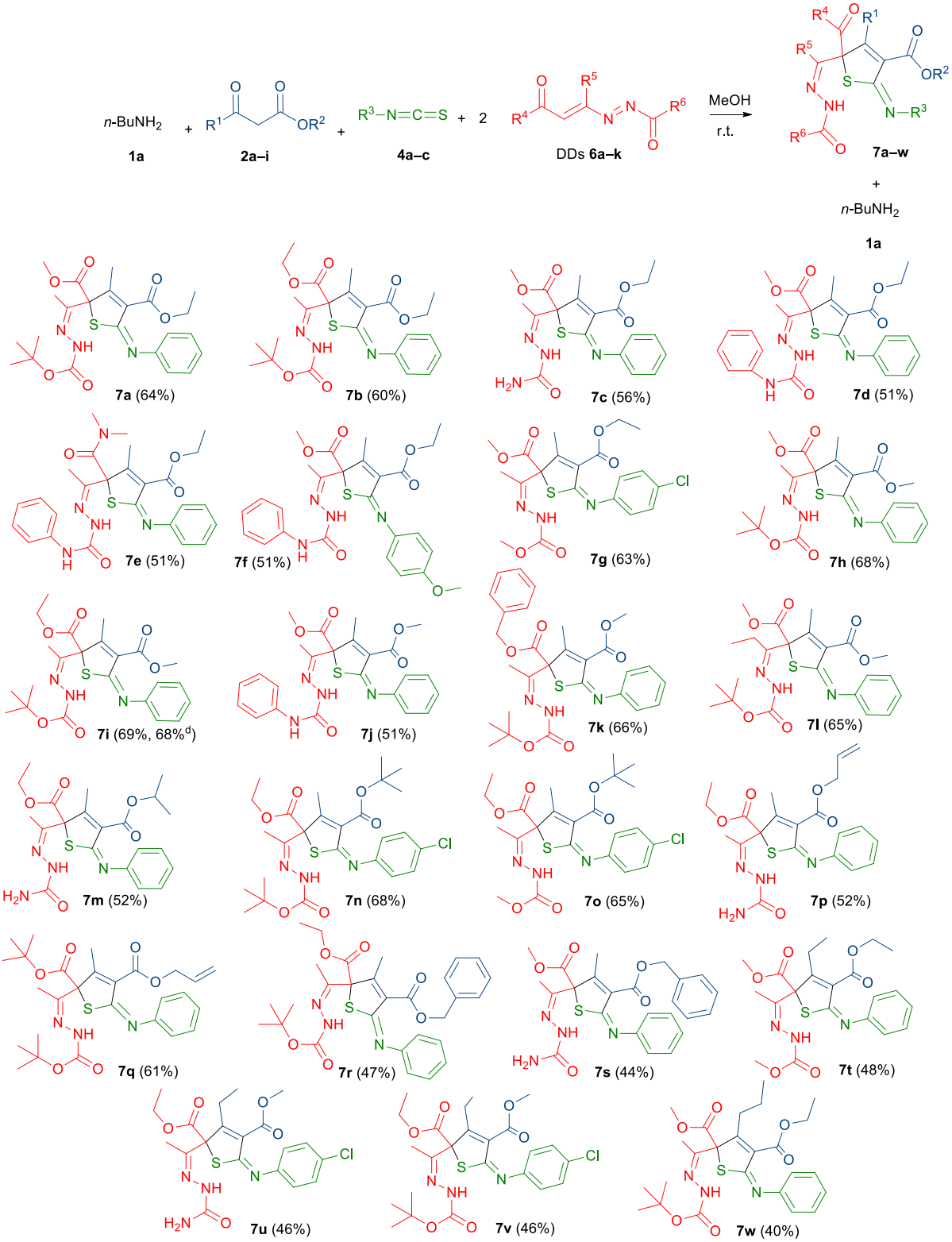
Entry	Solvent	T (°C)	molar ratio **5a**/**6a**	**7a** yield (%)[a,c]
1	SFC	rt	1:1	traces
2	SFC	80°C	1:1	traces
3[b]	DCM	rt	1:1	38
4[b]	THF	rt	1:1	27
5[b]	ACN	rt	1:1	33
6[b]	MeOH	rt	1:1	43
7[b]	MeOH	50°C	1:1	42
8[b]	**MeOH**	**rt**	**1:2**	**83**
9[b]	EtOH	rt	1:2	73
10[b]	EtOH	70°C	1:2	70
11[b]	DCM	r.t.	1:2	69

*[a]The reaction was performed at 0.5 mmol scale of ACT **5a**. [b]2 mL of solvent were employed. [c]Yields of isolated **7a** based on ACT **5a**.*

In SFC the low homogeneity affects the reaction and it furnishes a complicated mixture (Table 2, entries 1 and 2). So, different solvents, such as DCM, THF, ACN, MeOH were tested. In these latter cases, the main product was isolated and spectroscopic studies have revealed to be the corresponding 2,5-dihydrothiophene **7a**. In particular, the signal at 75.4 ppm in the ^{13}C NMR spectrum of the quaternary carbon in C2 position of the thiophene ring is diagnostic. Despite the low solubility of the ACT **5a** in MeOH, this solvent has furnished the best result. While the temperature does not affect the reaction, on the contrary to an increment of DDs equivalents corresponds an appreciable improvement in the final yield. This evidence can be explained considering that the *n*-butylamine **1a** released in the cyclization process gives a nucleophilic attack to the azo-ene system subtracting the DD **2a** from the reaction medium and producing the corresponding α-amino hydrazones **11** (Scheme 1).[18]

So, assembling all the informations collected on the individual reactions, we have finally conducted the one-pot synthesis on a representative model. *n*-Butyl amine **1a** (0.5 mmol.) was added to ethyl acetoacetate **2a** (0.55 mmol) under SFC. Within 0.5 h, the TLC analysis revealed the quantitative formation of the enamino ester **3**. To the reaction medium 1.5 mL of methanol and phenyl isothiocyanates **4a** (0.5 mmol.) were then added. The reaction was completed in 6.0 h and ACT **5a** appears as yellow precipitate. After the final addition of two equivalents of DD **6a**, the gradual dissolution of the yellow solid was observed, together with the disappearance of the typical red colour imparted to the solution by the conjugation of the azo-ene system. The reaction ended in 5.0 h furnishing the corresponding 2,5-dihydrothiophene **7a** in 64% yield (Table 3). Based on the success of the one-pot model, various β-ketoesters **2a–i**, isothiocyanates **4a–c**, and DDs **6a–k** were employed and the results are summarized in Table 3. Generally, the yields were good and it was possible to diversify two, one and three substituents on β-ketoesters, isothiocyanates and DDs, respectively, allowing wide molecular diversity. A gram scale synthesis of 2,5-dihydrothiophene **7i** was attempted by means of the here reported sequence and the target product was obtained in 68% yield, confirming the effectiveness of the synthetic protocol.

Table 3: Sequential four-component reaction of *n*-butyl amine **1a**, β-ketoesters **2a–i**, aryl isothiocyanates **4a–c**, and DDs **6a–k**: synthesis of 2,5-dihydrothiophenes **7a–w**.[a,b,c]

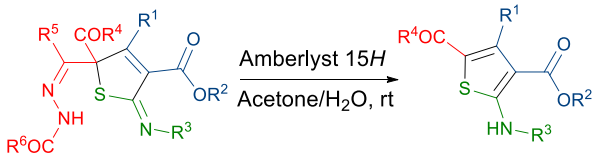


*[a]Reaction conditions: for a detailed experimental operation, see Supporting Informations. [b]Yields of isolated 2,5-dihydrothiophenes **7** based on n-butyl amine **1a**. [c]The reactions were performed at 0.55 mmol scale of β-ketoesters **2a–i**. [d]The reaction was performed at 10.0 mmol scale (1.161 g) of methyl 3-oxobutanoate **2b**.*

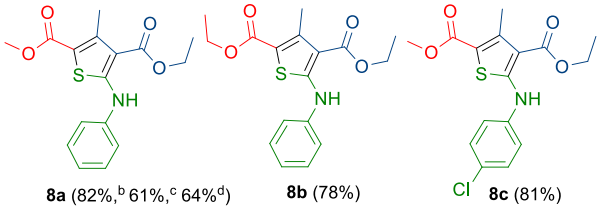
2,5-Dihydrothiophenes **7a–d,g–i,k,p–s,u,v** chosen as examples, were successively treated with Amberlyst 15*H* in a mixture of acetone/water to tentatively hydrolyse the hydrazone moiety.[19] Surprisingly, instead of the expected 2-

acetyl 2,5-dihydrothiophenes, the reactions have furnished in good yields the 5-amino thiophene-2,4-dicarboxylates **8a–j** (Table 4).

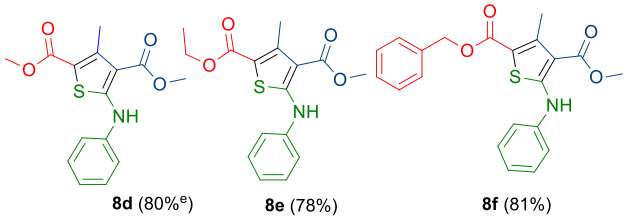
Table 4: Synthesis of 5-arylamino thiophenes **8a–j** by acidic treatment of 2,5-dihydrothiophenes **7**.[a]



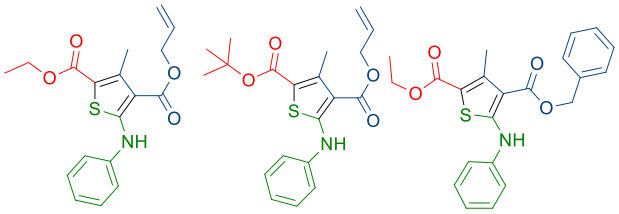
7a–d,g–i,k,p–s,u,v **8a–j**



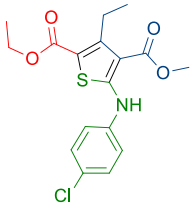
8a (82%,[b] 61%,[c] 64%[d]) **8b** (78%) **8c** (81%)



8d (80%[e]) **8e** (78%) **8f** (81%)



8g (83%) **8h** (70%) **8i** (81%,[f] 65%[g])



8j (68%,[h] 79% [i])

[a]*Yields of isolated 5-arylamino thiophenes* ***8a–j***. [b]*From* ***7a***. [c]*From* ***7c***. [d]*From* ***7d***. [e]*From* ***7h***. *From* ***7r***. [g]*From* ***7s***. [h]*From* ***7u***. [i]*From* ***7v***.

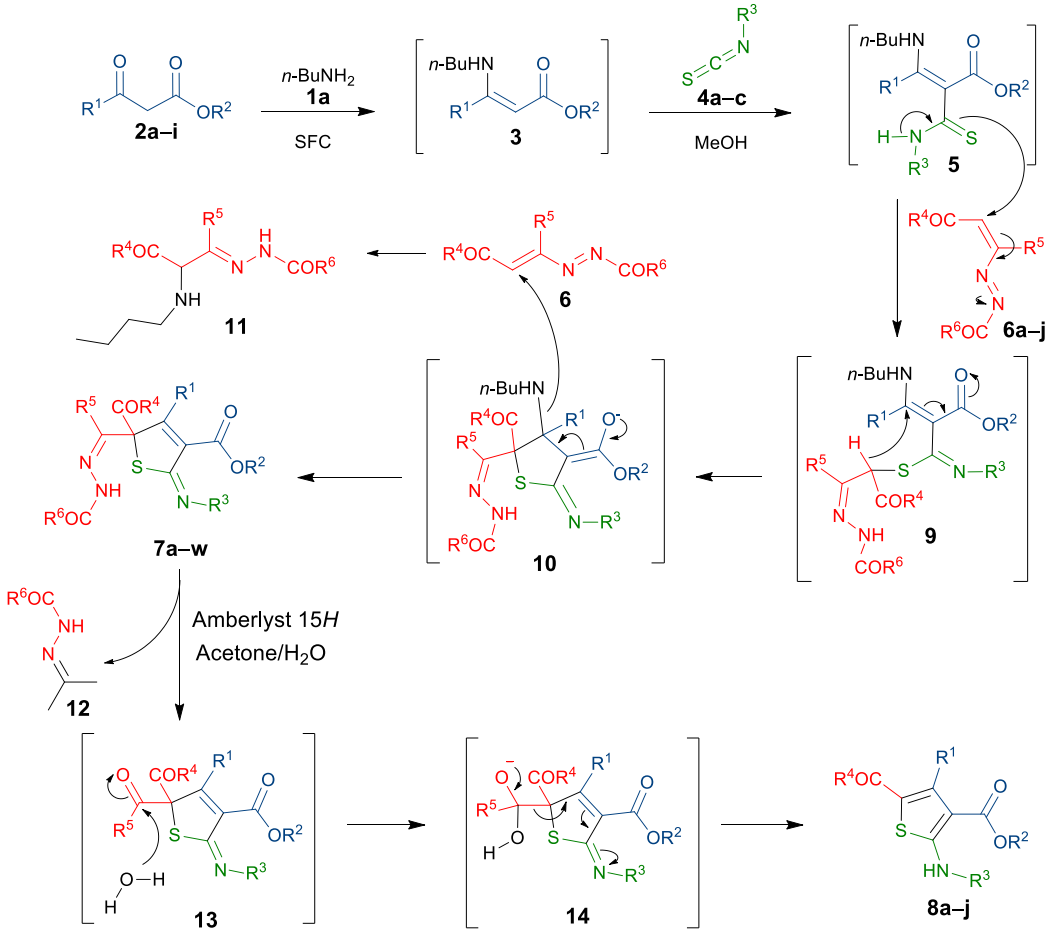
The structures of the aromatic compounds **8** were supported by spectroscopic data and unambiguously confirmed by comparison of diethyl 3-methyl-5-(phenylamino)thiophene-2,4-dicarboxylate **8b** with the same derivative previously synthesized by Kirsch.[20] It is noteworthy that this aqueous treatment is very selective leaving unaltered the other functional groups that are usually sensitive to acidic aqueous conditions such as Boc (see compound **8h**).

On the basis of this evidences, a plausible mechanism foresees the initial formation of the enamino ester intermediates **3**, that in turn react with the aryl-isothiocyanates **4** producing the ACTs **5** (Scheme 1). The subsequent cyclization process can involve a double Michael reaction. In fact, probably the sulphur of the ACTs **5** gives a first nucleophilic attack to the terminal carbon atom of the azo-ene system of the DDs **6** with formation of the α-thio-hydrazones intermediates **9**. The carbon in α to the hydrazone function is strongly activated and is able to give nucleophilic attack at the conjugated system deriving from the starting ACT with consequent formation of the tetrahydrothiophene intermediates **10**. The final conjugated elimination of the amino moiety affords the 2,5-dihydrothiophenes **7**. Curiously, in this formal [4+1][21] cyclization, there is an inversion of the roles of the two reagents: the ACT **5** behaves initially as a nucleophile and the DD **6** as an electrophile, while in the second step the carbon atom originally located in 4-position of the azo-ene system operates as nucleophile and the fragment deriving from the ACT as Michael acceptors. The acidic treatment in a mixture of acetone/water of 2,5-dihydrothiophenes **7** initially causes the expected hydrolysis of the hydrazone function producing the non-isolable 2-acyl 2,5-dihydrothiophenes **13**. The aqueous acidic medium favours a retro Claisen reaction that produces final 5-arylamino thiophenes **8a–j**. The aromatization is the driving force of this process. The hydrolysis of the hydrazone function of compounds **7** is confirmed by the isolation of traces of the *tert*-butyl 2-(propan-2-ylidene)hydrazinecarboxylate **12** obtained by the condensation between the *tert*-butyl hydrazinecarboxylate and acetone (Scheme 1).

Conclusion

In conclusion, we have developed with success a sequential MCR able to produce 2,5-dihydrothiophenes containing a quaternary centre alpha to the sulfur not easily obtainable by other methods. Importantly, this protocol provides wide and flexible substitution patterns in the final heterocycles allowing the planning "ab initio" of six different substituents by appropriately selecting the starting β-ketoesters, isothiocyanates or DDs. This opportunity, together with mild and simple reaction conditions (no catalysts, or dry solvents, or inert atmosphere), make this sequential MCR well suitable for the easy creation of broad libraries. Furthermore, the acidic treatment of the so obtained 2,5-dihydrothiophenes furnishes regioselectively the corresponding 2-aminothiophenes in good yields and under very mild conditions. Further studies to expand and apply these findings are on-going and the results will be reported in due of course.

Scheme 1: Plausible mechanism for the formation of 2,5-dihydrothiophenes **7a–w** and 5-arylamino thiophenes **8a–j**.



Experimental section

General procedure for synthesis of ethyl 3-(butylamino)-2-(phenylcarbamothioyl)but-2-enoate 5a under SFC conditions.
n-Butyl amine **1a** (0.5 mmol) was added to methyl 3-oxobutanoate **2a** (0.55 mmol) under solvent-free conditions at room temperature and vigorously stirred. After 0.5 h, phenyl isothiocyanate **4a** (0.50 mmol) was added and the reaction was stirred until the disappearance of the enamino ester **3** (6.5 h monitored by TLC). Then, the crude was chromatographed on silica gel column (elution mixture: cyclohexane:ethyl acetate) obtaining the corresponding ethyl 3-(butylamino)-2-(phenylcarbamothioyl)but-2-enoate **5a**.

General procedure for synthesis of 3-alkylamino-2-(carbamothioyl)but-2-enoates (ACTs) 5a–k
Butyl amine 1a (0.5 mmol) was added to β-ketoesters **2a–e** (0.55 mmol) under solvent-free conditions at room temperature and vigorously stirred. After 0.5 h aryl isothiocyanates **4a–c** (0.50 mmol) in MeOH (1.5 mL) were added and the reactions were stirred until the disappearance of the enamino esters 3 (6.0-18.0 h, monitored by TLC). The compounds **5a,c–j** crystallized directly from the reaction medium and were collected as pure products by filtration. From the mother solution, the methanol was evaporated under reduced pressure and the residue ACTs **5a,c–j** were purified by chromatography on silica gel column (elution mixture: cyclohexane:ethyl acetate) and successively crystallized in methanol. In the other cases, the reaction solvent was evaporated under reduced pressure and the final ACTs 5β,κ were purified by chromatography on silica gel column (elution mixture: cyclohexane:ethyl acetate) and successively crystallized in methanol.

One-pot procedure for synthesis of 2,5-dihydrothiophenes 7a–w.
n-Butyl amine 1a (0.5 mmol) was added to β-ketoesters **2a–i** (0.55 mmol) under solvent-free conditions and vigorously stirred at room temperature. After 0.5 h, aryl isothiocyanates **4a–c** (0.5mmol) in MeOH (1.5 mL) were added and the reactions were stirred until the disappearance of the enamino esters **3** (6.0–18.0 h, monitored by TLC). DDs **6a–k** (1.0 mmol) in MeOH (2.0 mL) were added to the reaction medium and magnetically stirred until the complete disappearance of the ACTs **5** (3.0–5.0 h, monitored by TLC). Then, the reaction solvent was evaporated under reduced pressure and the desired 2,5-dihydrothiophenes **7a–w** were purified by chromatography on silica gel column (elution mixture: cyclohexane:ethyl acetate).

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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Sequential multi component reaction between ketoesters, isothiocyanates and 1,2-diaza-1,3-dienes to create 2,5-dihydrothiophenes that can be converted into thiophenes.