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Original article

# Expeditious solvent-free synthesis of 1,3-thiazolanes *via* multicomponent reactions

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ABSTRACT

A series of 1,3-thiazolane derivatives have been synthesized *via* multicomponent reactions of activated acetylenes, primary amines and isothiocyanates in the presence of a catalytic amount of *N*-methylimidazole under solvent-free conditions.


## 1. Introduction

Multicomponent reactions (MCRs) are defined by three or more reactants joining in a one-pot procedure to afford a single product [1–4]. They are economically and environmentally useful because multi-step syntheses frequently produce a large amount of waste because the complex isolation actions often involve uncomfortable, toxic, and hazardous solvents after each step [5–8]. MCRs are absolutely suited for combinatorial library synthesis and are increasing utilized in discovery of new drugs and agrochemicals [9]. They represent a useful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [10,11]. Green chemistry holds significant potential not only for the reduction of byproducts, waste, and energy consumption but also in the expansion of new methodologies toward new materials, using existing technologies [12]. Medicinal and pharmaceutical chemistry possibly have the best chance to capitalize the green chemistry technologies [13]. For the perspective of the eco-friendly "green chemistry", a reaction should ideally, be conducted under solvent-free conditions with minimal or no side-product formation and with utmost atomeconomy [14].

Heterocycles are key compounds in the development of modern pharmaceutical chemistry, which is the reason why the design of amenable synthetic approaches for new heterocyclic systems is still significant challenge [15]. The thiazolium ring present in vitamin $B_1$ serves as an electron sink and its coenzyme form is important for the decarboxylation of keto-acids [16]. Several pesticides possessing a heterocycle with an S or an N atom are known in agriculture. A large numbers of heterocycles have emerged as active pharmaceutical ingredients in several drugs for their potential anti-inflammatory [17,18], anti-tumor [19] anti-hyperlipidemic [20], anti-hypertensive [21], anti-HIV infections [22], and several other biological properties [23,24].

Hence, we investigated a simple three-component reaction between activated acetylenic compounds, primary amines and isothiocyanates in the presence of a catalytic amount of *N*-methylimidazole under solvent-free conditions at room temperature which afforded 1,3-thiazolane derivatives **4** in good isolated yields. Propargylic esters gave lower yields (Scheme 1).

## 2. Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed

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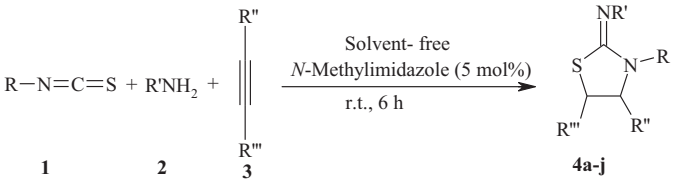



| Products | R | R' | R'' | R''' | Yield (%) |
|---|---|---|---|---|---|
| **4a** | Ph | Me | $CO_2Me$ | $CO_2Me$ | 75 |
| **4b** | 4-MeO-$C_6H_4$ | Et | $CO_2Me$ | $CO_2Me$ | 87 |
| **4c** | 4-MeO-$C_6H_4$ | *n*-Bu | $CO_2Et$ | $CO_2Et$ | 70 |
| **4d** | 4-Me-$C_6H_4$ | *t*-Bu | $CO_2Et$ | $CO_2Et$ | 75 |
| **4e** | 4-Br-$C_6H_4$ | Me | $CO_2Me$ | $CO_2Me$ | 80 |
| **4f** | 4-$NO_2$-$C_6H_4$ | Me | $CO_2Me$ | $CO_2Me$ | 75 |
| **4g** | *t*-Bu | Me | $CO_2Me$ | $CO_2Me$ | 78 |
| **4h** | Me | Et | $CO_2Et$ | $CO_2Et$ | 75 |
| **4i** | 4-MeO-$C_6H_4$ | Me | H | $CO_2Me$ | 56 |
| **4j** | Me | Me | H | $CO_2Et$ | 52 |

**Scheme 1.** Synthesis of compound **4** using primary amines, activated acetylenic compounds and isothiocyanates.

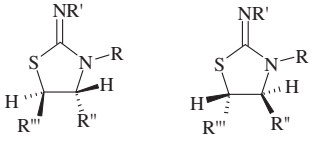


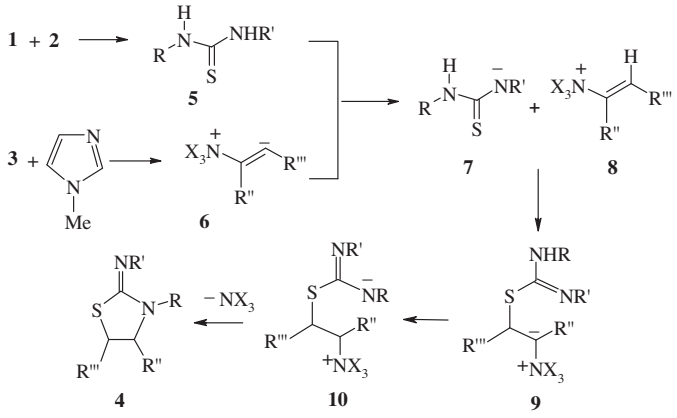
**Fig. 1.** Anti arrangement of **4**.

using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. $^1$H NMR and $^{13}$C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively, using $CDCl_3$ as a solvent and TMS as an internal standard or 85% $H_3PO_4$ as an external standard.

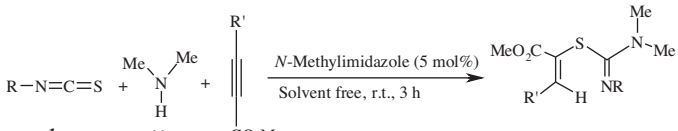
General procedure for preparation of compounds **4** and **12**: To a magnetically stirred mixture of activated acetylenes **3** (2 mmol) and *N*-methylimidazole (5 mol%) was added a mixture of isothiocyanates **1** and primary amines **2** or secondary amine **11** (2 mmol) at room temperature. The reaction mixture was then stirred. After the completion of the reaction [TLC (AcOEt/hexane 1:7) monitoring], 15 mL of $H_2O$ was poured into the reaction mixture. The solid residue was filtered and washed by cold diethyl ether to afforded pure compounds **4** and **12**.

## 3. Results and discussion

The structures of compounds **4a–j** were apparent from the $^1$H-NMR, $^{13}$C NMR and IR spectra which are in agreement with the proposed structures. For example, the $^1$H NMR spectrum of **4a** displayed two signals for vicinal methine protons at $\delta$ 4.78 and $\delta$ 4.92, which appeared as two doublets with $^3J_{HH}$ values of 12.4 Hz. The methoxy groups showed two singlets at $\delta$ 3.78 and $\delta$ 3.85. Observation of $^3J_{HH}$ = 12.4 Hz for the vicinal methine protons in **4a** indicates the dominance of anti arrangement. Since compound **4** possesses two stereogenic centers, two enantiomers with anti HCCH arrangements are possible (Fig. 1).




**Scheme 2.** Proposed mechanism for the synthesis of compound **4**.




| | R | R' | Yield (%) |
|---|---|---|---|
| **12a** | 4-MeO-$C_6H_4$ | $CO_2Me$ | 45 |
| **12b** | Me | H | 38 |

**Scheme 3.** Reaction of activated acetylenes, isothiocyanates and secondary amins in the presence of catalytic amount of *N*-methyl imidazole.

The carbonyl groups resonances in the $^{13}$C NMR spectra of **4a** appeared at $\delta$ 172.5 (C=O), $\delta$ 173.7 (C=O). Also the mass spectra of **4a** displayed the molecular ion peak with the correct *m*/*z* values.

A proposed mechanism for the formation of compound **4** is shown in Scheme 2. Apparently, the zwitterionic intermediate **6** that formed from the reaction of *N*-methylimidazole ($X_3N$) and the electron deficient acetylenic ester **3** is protonated by the intermediate **5** that was generated *in situ* from the reaction of primary amine **2** and isothiocyanate **1**, producing intermediates **7** and **8**. Nucleophilic attack of the conjugate base **7** on intermediate **8** leads to adduct **9**, which undergoes a proton transfer process to afford a new zwitterion **10**. Finally, intramolecular cyclization of **10** with the elimination of *N*-methylimidazole produces compound **4**.

Under similar conditions, these reactions proceed well with secondary amines but the yields of reactions are lower (Scheme 3).

The configuration of compound **12b** is confirmed by nuclear Overhauser effect (NOE) measurements. Thus, when the olefin signal was irradiated, the C=N$CH_3$ protons were enhanced by about 10%, while the N$(CH_3)_2$ protons showed no significant enhancement. Thus, the configuration was deduced from the NOE measurements and the same configuration was assumed for the other derivatives of **12**.

## 4. Conclusion

In conclusion, we found that the reaction of activated acetylenic compounds with isothiocyanates and primary amines in the presence of a catalytic amount of *N*-methylimidazole leads to a facile formation of some functionalized 1,3-thiazolanes under solvent-free conditions without using any additional catalyst. Also, butendioate and acrylate derivatives can be synthesized *via* the reaction of activated acetylenic compounds with isothiocyanate and secondary amines in the presence of a catalytic amount of *N*-methylimidazole.

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