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Azodicarboxylates: valuable reagents for the multicomponent synthesis of novel 1,3,4-thiadiazoles and imidazo[2,1-*b*][1,3,4]thiadiazoles

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ABSTRACT

Upon reaction of 4,5-disubstituted-*N*-arylaminoimidazole-2-thiones with isocyanides in the presence of azodicarboxylates (1.2 equiv) at rt, the imidazo[2,1-*b*][1,3,4]thiadiazoles were formed as the only reaction products in very good yields, whereas by using higher reaction temperatures, along with the imidazo[2,1-*b*][1,3,4]thiadiazoles, the three component reaction products, namely thiadiazoles, were also isolated, their formation being dependent on the 5-thione substituent. The thiadiazoles became the only reaction products, formed in very good yield by using 2 equiv of azodicarboxylates. The sodium cyanoborohydride and sodium borohydride reductions to thiadiazoles **11**, and **12** were also studied. Plausible mechanistic schemes for the formation of the thiadiazoles are proposed.

1. Introduction

The practically planar and rigid heteroaromatic imidazo[2,1-*b*][1,3,4]thiadiazole ring system is expected to have interesting physicochemical and biological properties, because of the presence of four heteroatoms and two condensed heterocycles with different π-conjugation. Indeed, imidazo[2,1-*b*][1,3,4]thiadiazole, but also thiadiazole derivatives, are known to possess interesting pharmacological properties, such as anticancer,[1,2] antitubercular,[3,4] antibacterial,[5,6] antifungal,[7] anti-inflammatory,[8] antimicrobial,[9,10] anticonvulsant and analgesic,[11] and antisecretory[12] activities.

The classical method for the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives involves reaction of 2-amino[1,3,4]thiadiazoles with appropriate α-haloketones,[13] whereas very recently a synthesis involving Suzuki–Miyaura cross-coupling reactions has been reported.[14]

As a continuation of our work on imidazole derivatives[15] and also on isocyanide multicomponent chemistry[16] we wish in the present work to describe our study concerning a one-pot method for the construction of the imidazo[2,1-*b*][1,3,4]thiadiazole scaffold by using imidazole-2-thiones, isocyanides, and azodicarboxylates as a basic catalyst. The subsequent transformation of the isolated imidazo[2,1-*b*][1,3,4]thiadiazole derivatives to new interesting multi-substituted [1,3,4]thiadiazoles by using excess of azodicarboxylates, acting as an electrophile in the presence of the five-membered heterocycle, is also described. Finally, the synthesis of the same multi-substituted [1,3,4]thiadiazoles through a one-pot multicomponent reaction between imidazole-2-thiones, isocyanides and excess of DEAD is reported.

2. Results and discussion

Initially, the reactivity of the imidazole-2-thione **1a** toward isocyanides was examined by reacting imidazolethione **1a** with cyclohexylisocyanide in the presence of a Lewis acid ($BF_3 \cdot Et_2O$) whereupon after stirring at ambient temperature for 4 h the imidazoformamidine **3a** was isolated in good yield (70%, Scheme 1).

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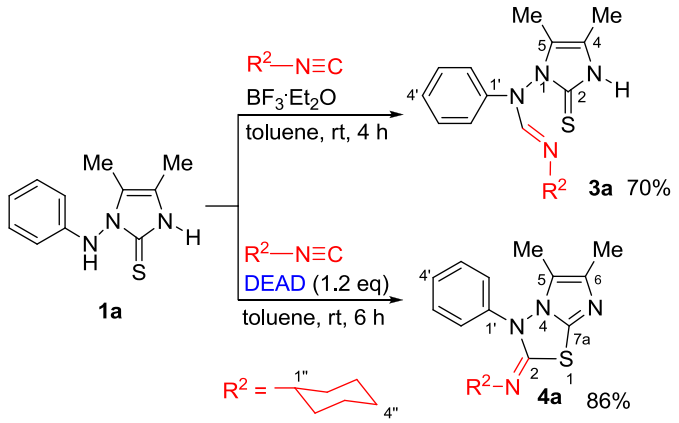
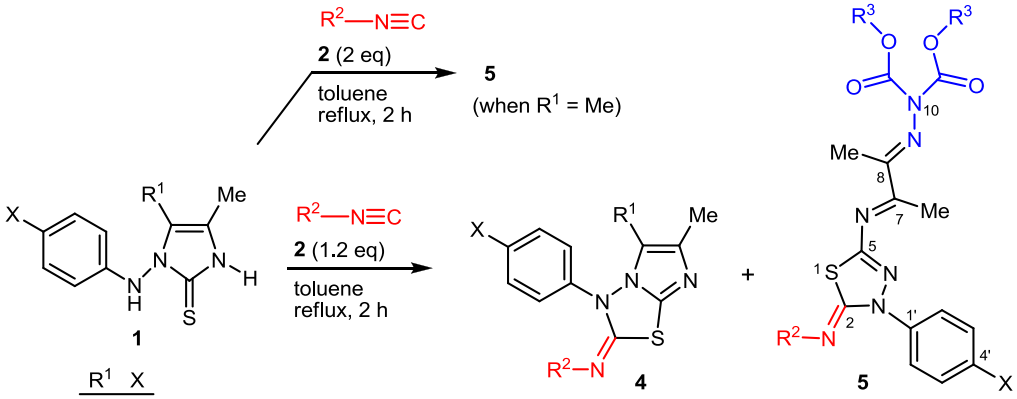


Scheme 1. Reaction of thione **1a** with cyclohexylisocyanide at ambient temperature in the presence or absence of azodicarboxylates.

An analogous reaction of benzothiazoles with isocyanides leading to different formamidine derivatives has very recently been reported in the literature.[17] In contrast, by using DEAD (1.2 equiv), 4,5-dimethyl-thione **1a**, and cyclohexylisocyanide, after stirring at room temperature for 6 h the imidazo[2,1-*b*][1,3,4]thiadiazole **4a** was isolated as the only reaction product in 86% yield (Scheme 1). However, when the same reaction was repeated in boiling toluene for 2 h, two products were formed, **4a** isolated in 55% yield and a three component product the tri-substituted thiadiazole **5a** isolated in 25% yield (Scheme 2). By using longer reaction times the yield of the three component product **5a** was slightly increased at the expense of **4a**, whereas by using 2 equiv of DEAD **5a** was isolated as the only reaction product in 87% yield. The reaction proceeded analogously by using other 4,5-dimethyl substituted thiones **1a**–**c** or other isocyanides, such as *tert*-butyl-, benzyl-, or phenylisocyanide and the results are shown in Scheme 2 and Table 1. However, when the 4-phenyl-5-methyl thione **1d** was used (entries 16 and 17, Table 1), even with 2 equiv of DEAD, regardless of the reflux time, the imidazothiadiazoles **4** were isolated as the only reaction products in high yields, and no trace of compounds **5** was detected. Analogous results were obtained by using DIAD instead of DEAD (entries 19–21, Table 1).

Finally, the imidazothiadiazole **4a** could be transformed into thiadiazole **5a** by refluxing with 1.2 equiv of DEAD in toluene for 2 h, and to imidazolethiones **6** after 5 h reflux in CH_2Cl_2 in the presence of acetic acid (Scheme 3).

Concerning the reaction mechanism, for the formation of the imidazothiadiazoles **4** it can be proposed that the zwitterion **7**, initially formed from the reaction between isocyanide and DEAD, abstracts the thione 2-NH proton forming finally intermediate **8**, which cyclizes to the end product **4** by loss of a diethyl (or diisopropyl) hydrazinedicarboxylate molecule (Scheme 4). However, by using excess of DEAD (2 equiv) and higher reaction temperatures (110 °C) a multicomponent reaction takes place, imidazothiadiazole **4** constituting in this case the reaction intermediate, formed during the first step of the reaction sequence. In the next step, an electrophilic attack of an azodicarboxylate molecule to the C5=C6 double bond of **4** leads initially to the formation of the dipolar intermediate **9** (Scheme 4), from which by formation of the diaziridine intermediate **10**, subsequent fission of the N4–C5 bond, and 'migration' of an ethoxycarbonyl group the end product **5** can be obtained. In favor of the proposed mechanism is the fact that the reaction proceeds only with the 5-methyl substituted thiones **1a**–**c**, whereas no reaction is observed using the 5-phenyl substituted thione **1d**. Most probably, steric hindrance but also extensive delocalization offered by the phenyl substituent renders the electrophilic attack of an azodicarboxylate molecule to C5=C6 double bond of **4f**–**g** unfavorable. An analogous electrophilic attack of a heterocyclic double bond to azodicarboxylate has also recently been



	R^1	X
a	Me	H
b	Me	Cl
c	Me	Me
d	Ph	H

	R^1	R^2	X
a	Me	*c*-Hex	H
b	Me	*t*-Bu	H
c	Me	Bn	H
d	Me	*c*-Hex	Cl
e	Me	*t*-Bu	Cl
f	Ph	*c*-Hex	H
g	Ph	*t*-Bu	H

	R^2	R^3	X
a	*c*-Hex	Et	H
b	*t*-Bu	Et	H
c	Bn	Et	H
d	*c*-Hex	Et	Cl
e	*t*-Bu	Et	Cl
f	*t*-Bu	Et	Me
g	Ph	Et	H
h	*c*-Hex	*i*-Pr	H
i	*t*-Bu	*i*-Pr	H
j	*c*-Hex	*i*-Pr	Cl

Scheme 2. Reaction of thiones with isocyanides and azodicarboxylates.