Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New thioureas based on thiazolidines with antioxidant potential

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ARTICLE INFO

Article history:
Received 24 September 2015
Accepted 9 October 2015
Available online xxxx

Keywords:
Thiazolidine
Thiourea
Thiosemicarbazide
Boric acid
Antioxidant

ABSTRACT

Thiazolidine and pyrrolidine compounds containing a thiourea moiety were prepared using boric acid as a coupling agent in a multicomponent methodology. In addition, the antioxidant activity, as reflected by free radical scavenging, was evaluated. Some compounds were selected and tested in different antioxidant experiments and all of them were shown to be useful for the prevention of oxidative stress in biological systems and thus capable of reducing cellular injury.

Introduction

Recently, compounds containing a thiourea moiety have received attention due their broad applications as organocatalysts[1] in different asymmetric chemical reactions, such as Michael,[2] Mannich,[3] Diels–Alder,[4] Friedel Craft[5] and other reactions. Furthermore, thiourea has been applied as selective chemical sensor for heavy metals[6] as well as other environmentally toxic compounds. Additionally this important class of compounds has shown important biological properties such as anti-cancer,[7] human anti-parasitic[8] and other activities. Thiourea derivatives are also very promising as building blocks for the synthesis of polymers[9] or as antioxidant[9a] components in polymer synthesis.

The classical methodologies for the synthesis of thioureas[1e,10] are very efficient, leading to good or excellent product yields. However, the classical methods involve the use of isothiocyanate, thiophosgene and thiocyanate salts, which are very toxic and harmful to the environment.[10] Therefore new methodologies have been developed to avoid using toxic starting materials while retaining good yields. The use of carbonylimidazole (CDI)[10d] as a substitute for thiophosgene, and the use of sunlight[10a] as the reaction promoter are examples of safe, cheap and environmental friendly methodologies.

In connection with this, thiazolidine derivatives have broad applicability in medicinal chemistry having anti-cancer,[11] anti-HIV[12e] and other important biological activities. Thiazolidine and its derivatives are important drug candidates, and they have already been screened against several disorders. Anti-convulsant, sedative, antidepressant, anti-inflammatory, anti-hypertensive, antihistaminic and anti-arthritic activities are a few among many other biologically important properties shown by these promising compounds.[12a] Recently, our group reported that besides their antioxidant properties Se-phenyl thiazolidine derivatives produced anti-nociceptive activity in experimental models and did not modify any biochemical or locomotor parameters or exploratory activities in mice.[12b–d] In addition, they also have been used as important chiral pools for the synthesis of several chiral ligands and organocatalysts.[13]

To the best of our knowledge, this is the first Letter in which a thiourea containing a thiazolidine moiety has been described. Therefore, it seems interesting to join together these two molecular fragments that have already proved separately to have important biological activities. Herein we describe our efforts on the development of a new methodology to synthesise new thioureas based on thiazolidine and pyrrolidine heterocycles through a multicomponent reaction using boric and boronic acids as coupling agents. An important feature of this new methodology is that it avoids the use of high-cost coupling reagents, protection groups or multiple steps to afford the final product.

Results and discussion

In 1996, Yamamoto described the synthesis of amides using boronic acids as coupling reagents and organic acids and amines as starting materials.[14a] An extension of this work was later

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http://dx.doi.org/10.1016/j.tetlet.2015.10.037
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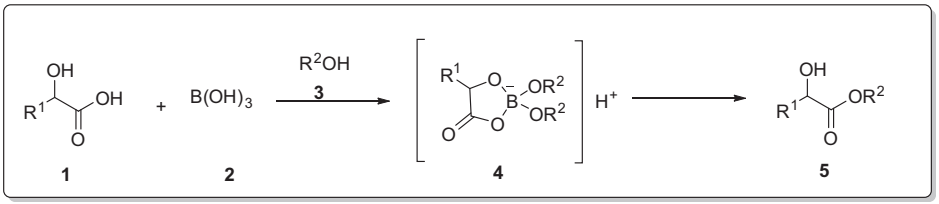
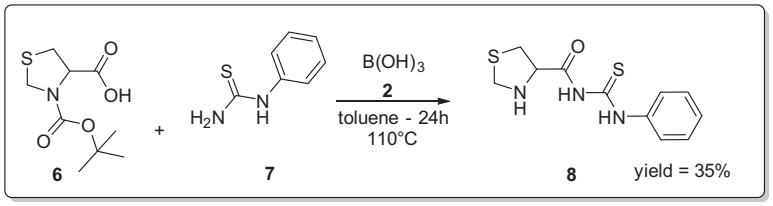
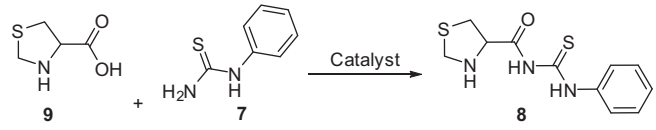


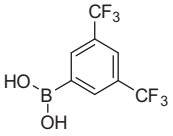
Scheme 1. Proposed mechanism for the boric acid-catalysed esterification.[13c]



Scheme 2. Coupling reaction between *N*-protected compound **6** and thiourea **7**.

Table 1
Catalytic activities of boronic and boric acid[a]

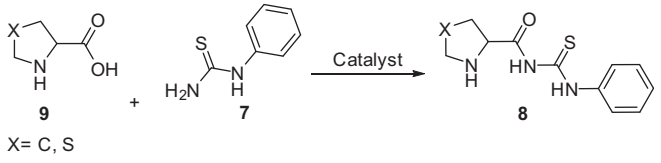


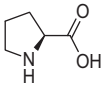
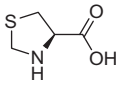
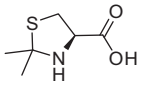
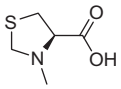
Entry	Catalyst	Catalyst load (mol %)	Solvent	Time (h)	Yield[b] (%)
1		10	Toluene	24	36
2		10	Toluene	24	33
3		10	*o*-Xylene	24	4
4		20	Toluene	24	41
5		30	Toluene	24	47
6		40	Toluene	24	45
7		30	Toluene	12	51
8		30	Toluene	6	30

[a] Experimental details: carboxylic acid (2.0 mmol), thiourea (2.2 mmol), solvent (10 mL).
[b] Isolated yields.

reported in which they used boronic acids for the coupling of α-hydroxy-acids and alcohols to afford esters in good to excellent yields, keeping the stereoisomeric information from the carboxylic acid.[14a,b] In both Letters the ordinary intermediate **4**, a bis-chelated compound from α-hydroxy-acid -to boron catalyst, was reported (Scheme 1).[14a–f]

Table 2
Thioureas synthesised by reaction coupling using boric acid[a]



Entry	Carboxylic acid	Load of catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1		30	Toluene	12	47
2		30	Toluene	12	51
3		30	Toluene	12	—
4		30	Toluene	12	—

[a] Experimental details: carboxylic acid (2.0 mmol), thiourea (2.2 mmol), toluene in refluxing (10 mL) using Dean–Stark apparatus, 12 h.
[b] Isolated yields.

Based on these previous results we envisioned the use of this methodology for the coupling of thioureas and thiazolidine carboxylic acids. As the starting point, we chose the thiazolidine-N-Boc-protected **6** as an analogous α-hydroxy-acid, to react with *N*-phenyl thiourea **7** using 10 mol % of boric acid **2** as the coupling reagent, in azeotropic reflux of toluene for 24 h. To our delight, we obtained the unprotected compound **8** at 35% yield in one single step (Scheme 2). This result suggests a dual role for the boric acid, where it can act as a coupling reagent as well as a deprotecting agent. With this result in hand, we performed another experiment, now using the thiazolidine–4-carboxilic acid **9** without the amino group protection under the same conditions and as expected, after 24 h, we obtained the compound **8** at 36% yield (entry 1—Table 1).

To establish the best reaction conditions we investigated the effect of catalyst loading, reaction time, solvent and temperature