L-Proline: An Efficient and Selective Catalyst for Transamidation of Thioamides with Amines

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Abstract
L-Proline catalysed transthioamidation of primary thioamides with amines under solvent-free conditions has been described. The transthioamidation is compatible with wide range of amines with yields up to 97%.

Keywords: Thioamides; Amines; L-Proline; Transthioamidation

Introduction
Thioamide is an important and useful functional group in both chemistry and biology. Thioamides are not only serve as versatile synthetic intermediates for the construction of pharmacologically important molecules containing nitrogen and sulfur heterocycles [1-7] but are also used as antitumor agents and enzyme inhibitors [8-10]. Thioamide based drugs such as ethionamide (ETH) and prothionamide (PTH) have been widely used for many years in the treatment of mycobacterial infections caused by Mycobacterium tuberculosis, M. leprae and M. avium complex infections [11,12]. Recently, functionalized-thioamide fluorescent dyes were also employed as metal ion sensors [13]. Diverse synthetic methods have been discovered for the synthesis of thioamides [14-23].

Transamidation is an attractive tool represents one of the most convenient and straightforward method, that would exchange the constituents of two different amide groups. Compared with transamination of amides with amines, the corresponding transthioamidations are rarely reported with rather limited substrate scope [24,25].

Most of the approaches for thioamide syntheses require transition metal catalysts to promote this transformation efficiently; also they suffer from inadequacies such as the expensive nature of catalyst, moisture and/or air sensitivity of Grignard reagents. Thus, the separation of metal catalyst from products, which is of particular importance for the synthesis of pharmaceuticals and fine chemicals because of their residual toxicity in the target compounds, is a central issue to consider.

In triggering chemical reactions. Particularly, L-proline has received much attention due to its dual role as a ligand and catalyst [31-34]. In view of the above perceptions, the development of benign and metal-free transamination procedures with high yield and selectivity is desirable. In continuation of our interest on the development of environment-friendly transamination catalysts [35-39], we wish to report a general L-proline-catalysed transthioamidation of primary amides with amines under solvent-free conditions [40]. To the best of our knowledge very rare reports available for the efficient transthioamidations under neat conditions [41].

Recently, organo catalysts have been employed in a variety of chemical transformations [26-30] and they dominate the natural world in triggering chemical reactions. Particularly, L-proline has received much attention due to its dual role as a ligand and catalyst [31-34]. In view of the above perceptions, the development of benign and metal-free transamination procedures with high yield and selectivity is desirable.

For the initial studies, we chose thioacetamide 1a and benzyl amine 2a as substrates to explore the transthioamidations using L-proline as catalyst (Figure 1). Initially, when 1a and 2a were reacted with 5 mol % of L-proline catalyst in water at 130°C in a sealed tube, the desired transthioamidations derivative 3a was isolated in 10% yield after 36 h (Figure 1, entry 1). In ethanol as solvent 19% of 3a was isolated (Figure 1, entry 2). Shifting to other organic solvents (toluene, DMF, DMSO, NMP and DMA), the yield of the product was varied between 42% and 85% (Figure 1, entries 3-7). To our delight, the reaction was also very facile under neat conditions at 130°C and gave 3a in 89% yield (Figure 1, entry 8). Further, no improvement in the yield was observed either...
by lowering the reaction temperature or by increasing the catalyst loading (Figure 1, entries 9–12). Under the same conditions, without catalyst only 43% of desired product 3a was isolated (Figure 1, entry 13). Increasing the reaction temperature yield was not improved; decomposition of the product was observed (Figure 1, entries 14 and 15). Transthioamidation was not efficient with other amino acid catalysts tested (Figure 1, entries 16–19).

With the set of optimized reaction conditions in hand, we moved on to investigate the scope of this metal-free transthioamidation. A series of amines were subjected to the transthioamidation of thioacetamide under these conditions (Figure 2). The reaction was found to be very facile with both electron-rich and moderately electron-deficient amines and produced corresponding transthioamidation products 3a–3f in moderate to good yield (46–89%). The transthioamidation was also efficient with variety of amines (alpha methyl, secondary benzyl, cyclic secondary, cyclohexyl, ary alkyl and long chain aliphatic amines) and provided the corresponding products 3g–3n in moderate to good yield (59%–86%). Similarly, transthioamidation of 2-(pyridin-2-yl) ethan-1-amine also gave 85% yield of desired product (3o).

To show the synthetic utility of this method, a variety of thioamides and amines were subjected to these optimized conditions (Figure 3). As expected, the transthioamidation of thiobenzamide with variety of amines [benzyl amines (electron-neutral, -rich,-deficient), alkyl aromatic, aliphatic, cyclic secondary amines and hetero amines] provided the corresponding products 5a–5m in moderate to good yields (33%–82%). Similarly, hetero amines like pyridin-2-ylmethanamine as well as heterothioamide were also gave the corresponding thioamidation products 5n and 5o in good yields. Based on our previous observations a plausible reaction mechanism has been proposed (Scheme 1). Initially, the reaction of thioamide with L-proline, generates the intermediate (I) through hydrogen bond formation. Subsequent addition of amine to the intermediate 1, will give the desired transthioamidation product with the elimination of ammonia.

Figure 1: Optimization of reaction conditions* (Reaction conditions: 1a (2 mmol), 2a (2 mmol), solvent (2 mL), in a sealed tube, isolated yield).

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol %)</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>yield (%)</th>
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<td>10</td>
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<tr>
<td>2</td>
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<td>EtOH</td>
<td>130</td>
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<tr>
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Figure 2: Scope for synthesis of thioamides using thioacetamide with different amines* (Reaction conditions: 1a (2 mmol), 2a (2 mmol), L-proline (11.5 mg), in a sealed tube, isolated yield).

Figure 3: Scope for transamidation of thioamides with various thioamides and amines* (Reaction conditions: 1a (2 mmol), 2a (2 mmol), L-Proline (11.5 mg), in a sealed tube, isolated yield).

**Conclusion**

In summary, we have reported the synthesis of variety of thioamides using easily available L-proline catalysed transamidation of various thioamides with amines under neat conditions. With this method a variety of corresponding thioamides were obtained in good to excellent yields under solvent-free conditions.

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References


40. Fioravanti S, Panis L, Pelagalli A, Pellacani L, Trulli L (2015) Synthesis of N-benzoylthioacetamide (3a): In a sealed tube, 2.0 mmol of 1a, 2.0 mmol of 2a and L-proline (11.5 mg) were stirred at indicated temperature for indicated reaction time (See Schemes 1-2 and Table 1). After being cooled to room temperature, the reaction mixture was extracted with DCM (3 X 20 mL). After removal of solvent, the crude reaction mixture left out was purified by recrystallization or silica gel (200-400 mesh) column chromatographic separation (dissolved in dichloromethane, eluted with dichloromethane and ethyl acetate). RSC Adv 5: 29312-29318.