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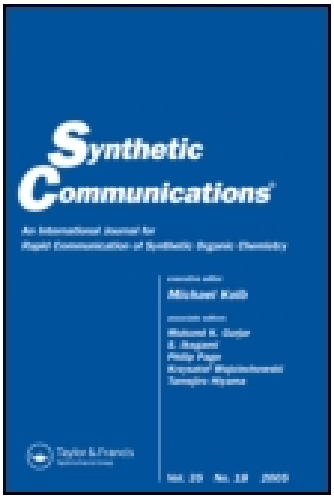

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DPT-Mediated Synthesis of 2-Aminoimidazolidin-4-ones from Thioureas Tethered to Amides

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DPT-MEDIATED SYNTHESIS OF 2-AMINOIMIDAZOLIDIN-4-ONES FROM THIOUREAS TETHERED TO AMIDES

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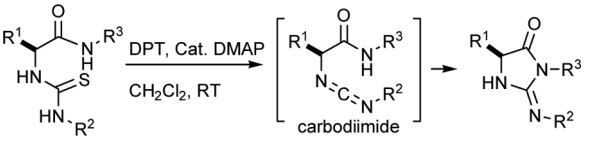
GRAPHICAL ABSTRACT



Abstract *2-Aminoimidazolidin-4-ones have been synthesized by using di-2-pyridyl thiocarbonate (DPT), taking the thioureas tethered to amides as the starting materials. Both the primary amides and secondary amides have been subjected to this cyclization method and in general this simple and convenient method was found to ensure good to excellent yields (81–99%).*

Keywords Aminohydantoin; aminoimidazolidinone; cyclization; synthesis

INTRODUCTION

In combinatorial synthesis, 2-amino-imidazolidin-4-one is a very attractive template because of its large number of possible substitution patterns and interesting combination of potential hydrogen bond donors and acceptors on a small five-membered ring system. This conformationally constrained single ring structure, with its guanidine- and imidazole-like moieties, can be exploited for achieving chemical diversity and also for generating a broad drug-like screening library. Thus a number of reports have been published mentioning the synthesis of diversified 2-aminoimidazolidin-4-ones, most of which are in the area of solid-supported synthesis[1–5] with few in solution-phase approaches.[6–9] These reported approaches studies have been observed to bear some common limitations, because they require use of relatively

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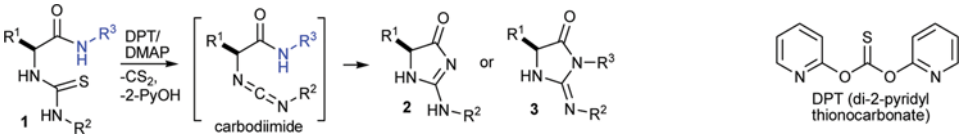
costly resin and use of protection and deprotection steps, with the related costs. Most of these methods require guanylation[2,4] by addition of secondary amine before the cyclization step, thereby generating 2-dialkylamino derivatives only, whereas the use of primary amines generated regeoisomers.[4,5] Some approaches required harsh reaction conditions,[2,3] extended reaction time,[1,2] or the use of heavy metals.[4] In some cases there were lower overall yields,[6] thereby imposing some more limitations. In the case of solution-phase synthesis, the aza-Wittig-type reactions[7,8] were also found to be limited to use of only the secondary amines just before cyclization, thereby generating 2-dialkylamino derivatives. Use of primary amines generated regeoisomers,[9] depending on the nucleophilicities and steric properties of the amines used.

RESULTS AND DISCUSSION

We have focused on the synthesis of 2-aminoimidazolidin-4-ones by a complementary approach to further diversify this attractive library using readily available starting materials. Our objective was to find a novel approach that offers greater yields while ensuring neutral reaction conditions; minimizes reaction steps, reaction time, and related costs; and minimizes racemization or regeoisomerization. Accordingly, commercially available L-amino acid amides and isothiocyanates were first converted to *N,N′*-disubstituted aryl (or alkyl) thioureas tethered to the primary (or secondary) amides, which were then treated with di-2-pyridylthionocarbonate (DPT) using a catalytic amount of DMAP to get the cyclized product **2** or **3** (Scheme 1).

While searching for the optimum reaction condition, cyclized product (**2a**) was obtained in 53% yield when run in CH_3CN for 6 h at room temperature (Table 1). Though a similar result has been observed from tetrahydrofuran (THF), greater yield (93%) was attained when the reaction was run in CH_2Cl_2 and the reaction was found to be completed within 3 hs. This ensured a short two-step process for getting the 2-aminoimidazolidin-4-one. Thus, relatively nonpolar solvent CH_2Cl_2 appeared as the most suitable (entries 1–3) one and accordingly was selected as the solvent for the next studies.

In reported studies[7] done using triphenylphosphine (as in aza-Wittig-type reactions) as the reagent in intermediate step(s), there was a need for recrystallization to remove the hazardous triphenylphosphine oxide. In our previous research work[10] for generating the 2-iminohydantoins using triphenylphosphine as the reagent, we faced similar hazards in some cases. In another aza-Wittig-type study, it was reported[9] that the generated iminophophorane was too labile to be isolated either by crystallization or by flash column chromatography and was observed to be hydrolized to the corresponding alpha-amino esters and triphenylphosphine oxides. In that



Scheme 1. DPT-mediated synthesis of 2-aminoimidazolidin-4-ones from thioureas tethered to amides.

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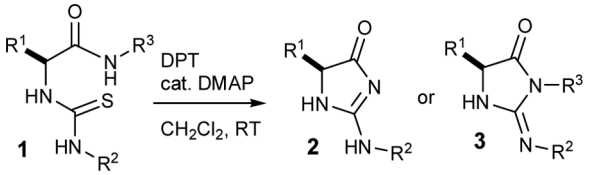
Table 1. DPT-mediated synthesis of 2-aminoimidazolidin-4-ones by thioureas tethered to amides



Entry	Substrate	R^1	R^2	R^3	Reaction time (h)	Products[a]	Yield (%)[b]
1	**1a**	*iso*-Butyl	Ph	H	3	**2a**	93
2	**1a**	*iso*-Butyl	Ph	H	6	**2a**	55[c]
3	**1a**	*iso*-Butyl	Ph	H	6	**2a**	53[d]
4	**1b**	H	Ph	H	3	**2b**	81
5	**1c**	CH_3	Ph	H	3	**2c**	89
6	**1d**	Bn	Ph	H	3	**2d**	91
7	**1e**	*iso*-Butyl	*n*-Pr	H	12	—	NR
8	**1f**	*iso*-Butyl	Ph	Ph	1.5	**3f**	99
9	**1g**	*iso*-Butyl	Ph	*n*-Pr	1.5	**3g**	96

[a]Compounds are known, and the spectral data are available in Refs. 10 and 11.
[b]Isolated yields.
[c]THF was used as solvent.
[d]CH_3CN was used as solvent.

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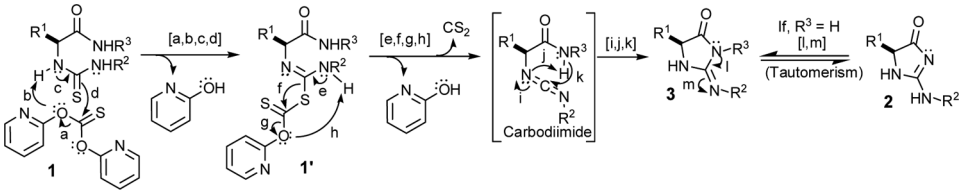
case, they were to run the next step without further purification to get the necessary carbodiimide. In another aza-Witting approach[7] to synthesize the 2-aminoimidazolidin-4-one from alpha-azidoesters, the stability of some carbodiimide intermediates were very uncertain, thereby demanding very careful control of the reaction and storage conditions. In our approach, the reaction was very clean, permitting smooth thin-layer chromatographic (TLC) monitoring. At the same time DPT gave acidic 2-hydroxypyridine as the by-product (Scheme 1), offering very convenient workup process (simple washing with saturated $NaHCO_3$ solution offered the desired product).

As can be shown in entries 4–6 (Table 1), the *N,N′*-disubstituted phenyl thioureas (**1b**–**1d**) were smoothly cyclized to the corresponding cyclized products (**2b**–**2d**) within 3 h in excellent yields (81–91%), thus indicating satisfactory conversion to the corresponding carbodiimide intermediates, which spontaneously cyclized to the desired 2-aminoimizazolidin-4-ones. These represent the excellent scope of generating the 2,5-disubstituted 2-aminoimidazolidin-4-one libraries by exploitting DPT-mediated cyclization of thioureas tethered to amides.

However, in the case of simple *N,N′*-dialkyl substituted thioureas (**1e**), disappointingly, there was no reaction (entry 7, Table 1) even after running the reaction for 12 h. This indicates that if both the R^1 and R^2 are alkyl substituents, then DPT cannot generate the intermediate carbodiimide and thus is not capable of inducing the subsequent cyclization. This can be further justified by entries 8 and 9, where the presence of aromatic rings favored the carbodiimide generation, thereby ensuring nearly quantitative yields (99% and 96%). These approaches offered a better method when compared to the cyclization of similar thioureas by using $CBr_4/Ph_3P/DIPEA/CH_2Cl_2$.[10] Besides, DPT-mediated cyclization demanded much shorter



Scheme 2. Plausible mechanism of DPT-mediated synthesis of 2-aminoimidazolidin-4-ones from thioureas tethered to amides.

reaction time (1.5 h) as compared to that needed (6 h) for cyclization by $CBr_4/Ph_3P/DIPEA/CH_2Cl_2$. Thus these DPT-mediated cyclization represents an additional rapid and convenient approach for generation of diversified 2,3,5-trisubstituted 2-aminoimdazolidin-4-one libraries from thioureas tethered to secondary amides.

In cases where there are both the thiourea and urea groups in the same molecule, some reported[10] agents such as $CBr_4/Ph_3P/DIPEA/CH_2Cl_2$ or $CCl_4/Ph_3P/DIPEA/CH_2Cl_2$ cannot be used to induce the selective cyclization as they can offer the cyclized products by exploiting either of these functional groups, thereby offering regeoisomers or simply undesired products. However, DPT-mediated cyclization ensures the expected selectivity as it can exploit only the thiourea moieties because it cannot generate the carbodiimides but not from the ureas.

Because all the reactions were run at room temperature, this DPT-mediated approach may be a good replacement for the those procedures where the methods were not suitable to generate the desired 2-aminoimidazolidin-4-ones simply because of the harsh reaction conditions. At the same time, this neutral reaction condition might be an excellent option for cases where the reacting intermediates or products might have acid-sensitive or base-sensitive functional groups or moieties.

While predicting the mechanism of this cyclization, the thiourea **1** is first converted (Scheme 2) to the conjugate **1′** through [a,b,c,d] releasing one molecule of 2-hydroxypyridine. This intermediate is again passed through [e,f,g,h] to generate the carbodiimide, thus releasing one more 2-hydroxypyridine molecule and additionally one molecule of carbondisulfide. This carbodiimide is then spontaneously undergone through [i,j,k] to generate the 2-iminoimidazolidin-4-one **3**. Finally if the thiourea used was a primary amide (i.e., R^3 is H), this final compound again undergoes the favoured tautomerism through [l,m] to generate the desired 2-aminoimidazolidin-4-one **2**.

EXPERIMENTAL

General Procedure for Synthesizing 2-Aminoimidazolidin-4-ones from Thioureas

The DPT (1.1 mmol) and a catalytic amont of DMAP were added to the thiourea (1.0 mmol) in dry CH_2Cl_2 (2 mL). The mixture was then stirred for 1.5–6 h at room temperature and concentrated in vacuo. The residue was diluted with water and EtOAc, and the organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to get the crude

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product, which was purified by flash column chromatography using increasing polarity gradients of hexane/EtOAc/CH_2Cl_2. Spectral data are available in Refs. 10 and 11.

CONCLUSION

We have developed a simple and convenient approach for the synthesis of 2-aminoimidazolidin-4-ones from thioureas with DPT under neutral reaction conditions, thereby imposing an excellent complementary approach for generating diversified 2-aminoimidazolidin-4-one libraries. Further examinations of the scope of this method for the synthesis of library are currently under way in our laboratories.

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SUPPLEMENTARY DATA

Full experimental detail of cyclization of the thioureas tethered to amide, ^{1}H NMR spectral data of the thioureas, analytical and spectral data, along with ^{1}H NMR and ^{13}C NMR spectra of the cyclized products for this article can be accessed on the publisher's website.

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