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Synthesis and applications of 4-substituted 1-(4-iodophenyl)pyrrolidine-2,5-diones

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ABSTRACT

The synthesis of 4-substituted 1-(4-iodophenyl)pyrrolidine-2,5-dione derivatives was achieved through an addition reaction between amines and a thiol in the presence of PMDTA as a base and a copper salt. The derivatives containing a terminal acetylene moiety were converted to the corresponding 1,4-triazolyl derivatives. The 1-(4-iodophenyl)pyrrolidine-2,5-dione derivatives were functionalized through oxidation alkylation and allylation reactions. In general, the compounds were obtained in moderate-to-good yields.

Introduction

Nitrogen-containing heterocycles are extensive in a large number of natural and unnatural products.[1] Pyrrolidines and piperidines represent some of the most common core heterocyclic structures among these series and a number of synthetic methodologies have been utilized for their synthesis or the preparation of their derivatives.[2] In this field, aminopyrrolidines are important synthetic targets and polyhydroxylated aminopyrrolidines have attracted interest because of their potential role as glycosidase inhibitors.[3] Oxopyrrolidines and 3-aminopyrrolidines are used as chiral ligands[4] and building blocks for the synthesis of bioactive compounds.[5,6]

3-Aminopyrrolidine derivatives (**1**) are used as GlyT1 inhibitors for the treatment of diseases such as neuro-/psychiatric disorders and pain.[7] Oxopyrrolidine derivatives (**2**) are inhibitors of methionine amino peptidase (MetAP-2) and can also be used for the treatment of tumors.[8] Aminopyrrolidine derivatives (**3**) are also useful intermediates for antibacterials[9] (Fig. 1).

Similarly, 3-mercaptooxopyrrolidines have also great importance as proteomic linkers.[10] Advances in thiol-ene chemistry[11] have been rapid over the last decade, as the highly versatile reactivity of thiols with alkenes has been utilized across multiple areas of macromolecular,[12] biomolecular,[13] and materials chemistry.[14]

Zhou et al. developed a small molecular targeted contrast agent CREKA-Tris(Gd-DOTA)$_3$ for effective molecular MRI of a cancer biomarker that is abundant in the tumor microenvironment. CREKA-Tris(Gd-DOTA)$_3$ resulted in strong and prolonged tumor contrast enhancement. The small molecular peptide-targeted MRI contrast agent holds great promise for clinical cancer molecular imaging.[15]

Styslinger et al. presented a method that allows the facile site-selective glycosylation of proteins with carbohydrates of variable molecular weights (*MW*s). To demonstrate the usefulness of this technology, hemoglobin (Hb) was site-selectively glycosylated with a series of carbohydrates of increasing *MW* (from 504 to ~10,000). Hb was selected on the basis of the vast wealth of biochemical and biophysical knowledge present in the literature and because of its use as a precursor in the synthesis/formulation of artificial red-blood-cell substitutes[16] (Fig. 2).

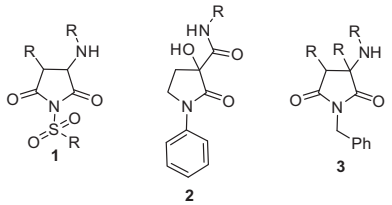

Figure 1. Structures of compounds **1**–**3**.

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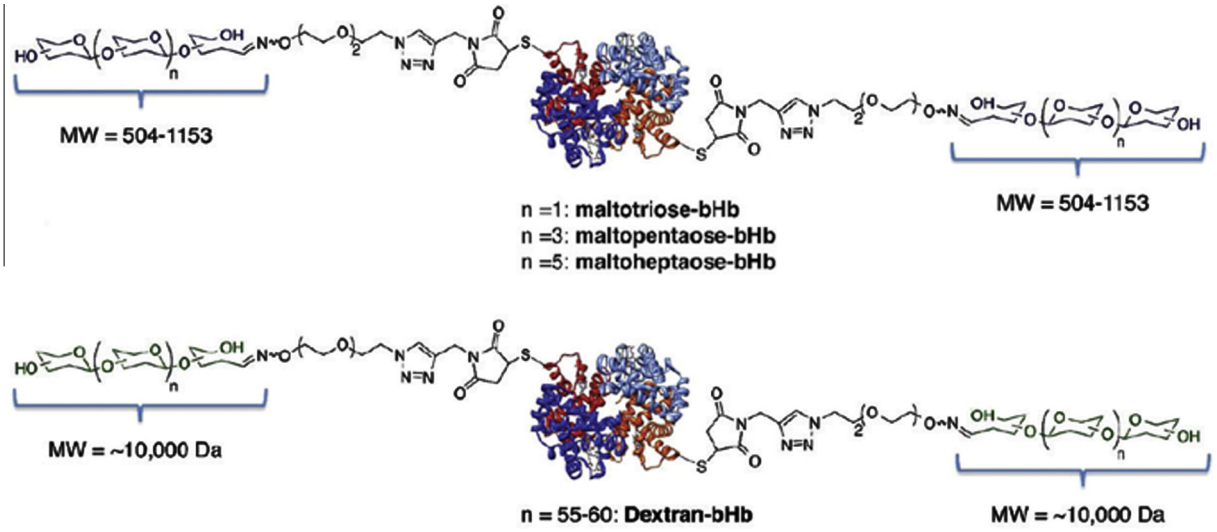


Figure 2. Structure of mercapto oxopyrrolidine oligosaccharides.

Typical routes to aminopyrrolidines employ resolution of racemates,[17] radical cyclization,[18] or a chiral pool with carbohydrates[19] and amino-acid derivatives[20] as starting materials.

According to previously published reports, 3-aminopyrrolidines are prepared through an aza-Michael addition, either from maleimide with amines using a base such as TMEDA (tetramethylethylenediamine) or TMCDA (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1, 2-diaminocyclohexane)[21] or from aspartic acid.[22] There are few articles reported, but similar 3-aminopyrrolidine compounds are commercially available. There are many reports on the Michael addition of amines to electron-deficient alkenes.

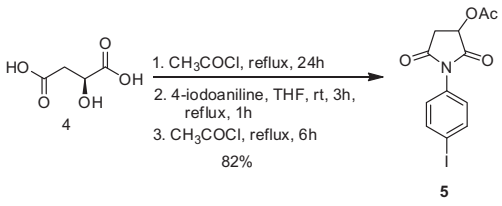
These conjugate additions are carried out in the presence of a strong base or acid.[23] To avoid these harsh conditions, a number of milder procedures have been developed using reagents such as $SnCl_4/FeCl_3$,[24] $InCl_3$,[25] $CeCl_3{\cdot}7H_2ONaI$,[26] $Yb(OTf)_3$,[27] $Cu(OTf)_2$,[28] CAN (cerium ammonium nitrate),[29] $Bi(NO_3)_3$,[30] $Bi(OTf)_3$,[31] $LiClO_4$,[32] KF/alumina,[33] SmI_2,[34] $Cu(acac)_2$/ionic liquid,[35] ionic liquid/quaternary ammonium salt in water,[36] boric acid in water,[37] β-cyclodextrin,[38] $ZrOCl_2{\cdot}8H_2O$,[39] borax,[40] bromodimethylsulfonium bromide,[41] $[HP(HNCH_2CH_2)_3N]NO_3$,[42] cationic palladium complexes,[43] $MnCl_2$,[44] DBFOX-Ph(R)·$Ni(ClO_4)_2{\cdot}6H_2O$,[45] and so forth.

In our previous report, we prepared maleimide from malic acid.[46] In the present investigation, we explore a simple and general procedure for the generation of maleimide and the conjugate addition of a variety of amines in the presence of a catalytic amount of copper(I) iodide in THF in a one-pot reaction.

Results and discussion

We obtained 1-(4-iodophenyl)-2,5-dioxopyrrolidin-3-yl acetate (**5**) from L-malic acid according to our reported protocol,[46] in which L-malic acid was treated with acetyl chloride before 4-iodoaniline was added at room temperature over 3 h, after which it was refluxed for 1 h and again treated with acetyl chloride to give imide (**5**) in 82% yield (Scheme 1).

With the starting material, 1-(4-iodophenyl)-2,5-dioxopyrrolidin-3-yl acetate, in hand and with the intention of obtaining the target product by Buchwald–Hartwig methods, we surveyed various catalysts, temperatures, and bases for the nucleophilic substitution, but, to our surprise, this methodology failed to yield the target product because, at elevated temperature, the reacting amines were active sites for addition instead of substitution reactions.



Scheme 1. Synthesis of 1-(4-iodophenyl)-2,5-dioxopyrrolidin-3-yl acetate (**5**).

Buchwald performed the iodo substitution with an amine using CuI[47] and Hartwig later presented the same substitution with palladium.[48] Initially, we used CuI (5 mol %), employing Et_3N at 70 °C for 24 h, and we obtained a mixture of products (Table 1, entry 1) instead of getting the target product (Scheme 2).

Then, we used different palladium (Pd) and palladium–copper (Pd/Cu) catalysts at 70 °C for 24 h with 2.5 equiv of amine. In the next strategy, 1.2 equiv of amine and PMDTA (*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine) were used with Pd and Pd/Cu catalysts at 70 °C for 24 h and, in these cases, compound **7** was the major product, which inspired us to increase the yield further (Table 1, entries 8 and 9). As shown in Table 1, entry 9, the yield of product **7** was 48%; when using $Pd(PPh_3)_2Cl$ (5%) + CuI (5%) as the catalyst, decreasing the reflux time to 3 h, and using DMF as the solvent, the yield could be increased to 56% (Table 1, entry 10).

Next, using $Pd(PPh_3)_2Cl$ (5%) + CuI (5%) catalysts and PMDTA at room temperature in the presence of DMSO or DMF as the solvent, the reaction resulted in yields of 55% and 58% (Table 1, entries 11 and 12, respectively). But, when CuI (30 mol %) was used under the same conditions, it resulted in a 63% yield (Table 1, entry 13), which was attributed to Cu–PMDTA complexation and the generation of maleimide and then addition of the amine, as presented in our previous investigation.[46] Then, we tried to put the catalyst (CuI) and PMDTA in the reaction with the starting material and stirred it for 2 h to generate maleimide and then addition of the amine proceeded overnight, which gave a good yield of 70% through a one-pot, two-step reaction and allowed the starting material to be recovered (Table 1, entry 14).

Using the above conditions, the bases PMDTA, Et_3N, and DIPEA were used, leading to yields ranging of 65–71% (Table 1, entries 15 and 16). The best result was obtained when PMDTA (1 equiv) and Et_3N (1 equiv) were used together as the base, giving an 88% yield