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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).

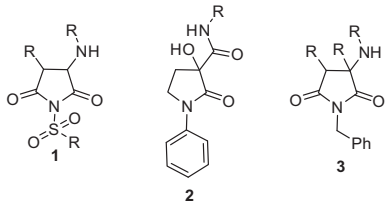

Figure 1. Structures of compounds **1**–**3**.

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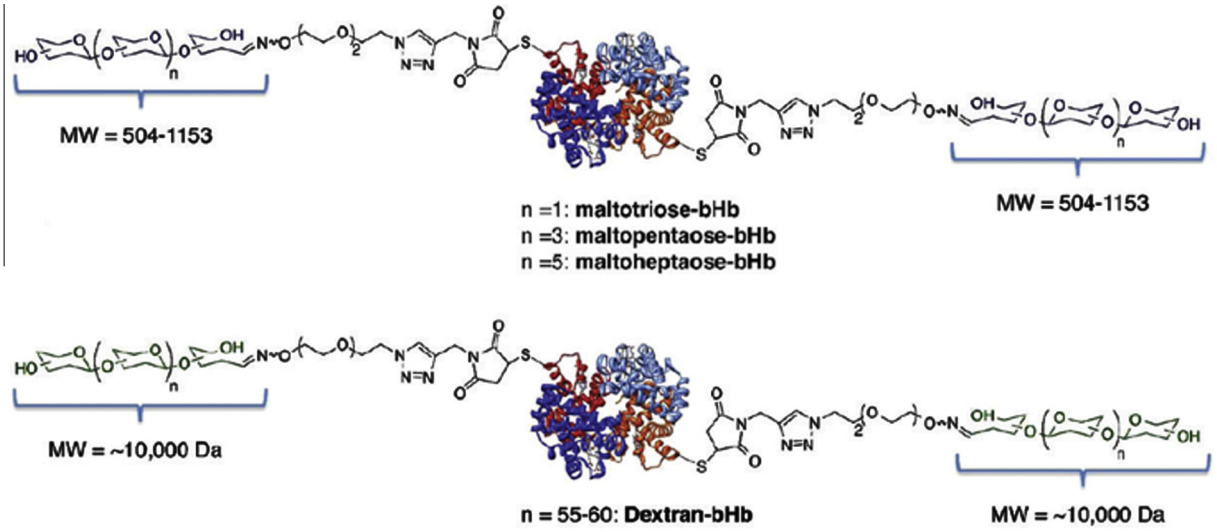


Figure 2. Structure of mercapto oxopyrrolidine oligosaccharides.

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.

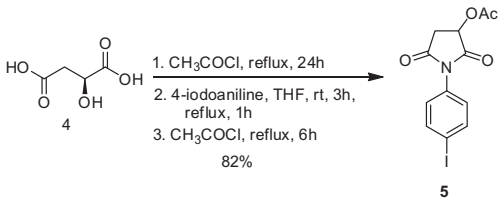
These conjugate additions are carried out in the presence of a strong base or acid.[23] To avoid these harsh conditions, a number of milder procedures have been developed using reagents such as $SnCl_4/FeCl_3$,[24] $InCl_3$,[25] $CeCl_3{\cdot}7H_2ONaI$,[26] $Yb(OTf)_3$,[27] $Cu(OTf)_2$,[28] CAN (cerium 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**).

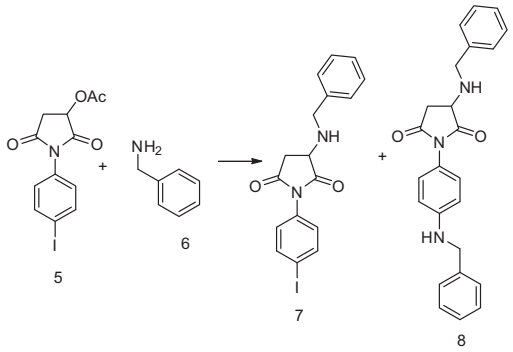
Buchwald performed the iodo substitution with an amine using CuI[47] and Hartwig later presented the same substitution with palladium.[48] Initially, we used CuI (5 mol %), employing Et_3N at 70 °C for 24 h, and we obtained a mixture of products (Table 1, entry 1) instead of getting the target product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

Table 1
Optimization of the reaction conditions

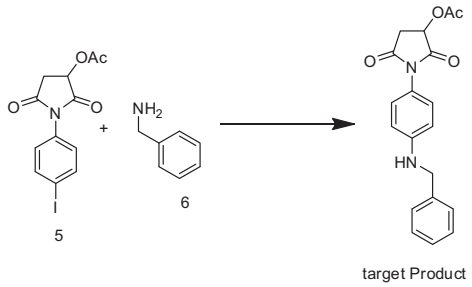


Entry	Catalyst	Base	Solvent	Yield (%) **7**/**8**
1	CuI (5%)	Et_3N	DMSO	25:15[a,c,f,g]
2	Pd/Fe_2O_3 (5%)	Et_3N	DMSO	23:15[a,c,f,g]
3	$Pd(OAc)_2$ (5%)	Et_3N	DMSO	29:14[a,c,f,g]
4	$Pd(PPh_3)_2Cl$ (5%)	Et_3N	DMSO	28:15[a,c,f,g]
5	$PdCl_2$ + CuI (5%)	Et_3N	DMSO	30:16[a,c,f,g]
6	$Pd(PPh_3)_2Cl_2$ (5%) + CuI (5%)	Et_3N	DMSO	29:18[a,c,f,g]
7	CuI (5%) + Proline (10%)	K_3PO_4	DMSO	31:12[a,c,f,g]
8	$Pd(OAc)_2$ (5%) + CuBr (5%)	PMDTA	DMSO	38:14[a,c,g]
9	$Pd(PPh_3)_2Cl$ (5%) + CuI (5%)	PMDTA	DMSO	48:10[a,c,g]
10	$Pd(PPh_3)_2Cl$ (5%) + CuI (5%)	PMDTA	DMF	56:0[a,c,h]
11	$Pd(PPh_3)_2Cl$ (5%) + CuI (5%)	PMDTA	DMSO	55:0[b,d,i]
12	$Pd(PPh_3)_2Cl$ (5%) + CuI (5%)	PMDTA	DMF	58:0[b,d,i]
13	CuI (30%)	PMDTA	THF	63:0[b,d,i]
14	CuI (30%)	PMDTA	THF	70:0[b,d,i]
15	CuI (30%)	Et_3N	THF	71:0[b,d,i]
16	CuI (30%)	DIPEA	THF	65:0[b,d,i]
17	CuI (30%)	PMDTA (1 equiv) + Et_3N (1 equiv)	THF	88:0[b,d,i]
18	CuI (30%)	PMDTA (1 equiv) + Et_3N (1 equiv)	THF	60:0[b,e,h]
19	—	PMDTA	THF	Traces
20	CuI	—	THF	nr

[a] Starting material, amine, catalyst, and base added at the same time.
[b] Starting material, catalyst, and base added at the same time and stirred for 2 h and then amine was added and left stirring for overnight.
[c] Temperature, entries 1–9 = 70 °C.
[d] Temperature, entries 11–12 = rt.
[e] Temperature, entry 22 = ultrasonic bath rt.
[f] Temperature, entries 8–20 = 1.2 equiv. benzylamine.
[g] Reaction time, entries 1–9 = 24 h.
[h] Reaction time, entry 10 = 3 h.
[i] Reaction time, entries 11–17 = 18 h.

(Table 1, entry 17). Similarly, the reaction was carried out with ultrasonication, but, in this case, the yield decreased (Table 1, entry 18). The use of CuI and PMDTA is of paramount importance. In the absence of CuI only traces of the desired product was observed and in the absence of PMDTA no reaction occurred (Table 1, entries 19 and 20).

After optimizing the conditions, we synthesized a series of 1-(4-iodophenyl)-3-(*R*-amino or *R*-thio)pyrrolidine-2,5-dione derivatives (Table 2, entries 1–14).[49] As shown in Table 2, primary and secondary amines react smoothly with yields ranging from 58% to 88%; similarly, a thiol gave an 86% yield (Table 2, entry 14) and alcohols were found to be unreactive. It was found that, when the reaction was carried out with substituted anilines containing



Scheme 2. Buchwald cross-coupling reaction.

nitro, *p*-methoxy, and fluorine groups, there was no addition reaction to the formed maleimide. Similarly, when hydroxy-containing reactants were surveyed, there was no observed reactivity (Table 2, entry 2). Also, amino acids were evaluated for the addition reaction, but showed no reactivity (Table 2, entry 6).

The reaction carried out with primary aliphatic amines worked well with almost the same yields ranging from 78% to 83% (Table 2, entries 11–13). Aliphatic amines containing branched alkyl groups gave good yields from 66% to 75% (Table 2, entries 5–7). Similarly, a primary-amine containing cyclic moiety gave an 83% yield (Table 2, entry 13). The yield dropped when diamine was reacted, giving a yield of 58% (Table 2, entry 4). For secondary amines, the yields were 70% and 65% (Table 2, entries 1 and 3, respectively).

We also tried to further investigate the scope for the one-pot synthesis of triazole. As mentioned above, the starting material was dissolved in THF, the catalyst (CuI) was added, and then the base PMDTA was added drop-wise, after which Et_3N was added in the same way and stirred for 2 h to generate maleimide; then, the addition reaction of amine to the formed maleimide proceeded overnight before the azide was added and stirred for a further 6 h. All of the synthesized triazoles have good yields, confirming the successful one-pot, three-step reaction (Table 3, entries 1–5).[46,50]

Initially, when aliphatic azides were employed as the substrates, the products were obtained in good yields 73%, 75%, and 68% (Table 3, entries 1, 2, and 5, respectively). Although only two aromatic azides were used, it appears that the presence of an electron-donating or electron-withdrawing group influences the yield of the reaction. The aromatic azide containing the *p*-methoxy substituent resulted in a yield of 77% and the aromatic azide containing *p*-iodine afforded the product in a 53% yield (Table 3, entries 3 and 4, respectively).

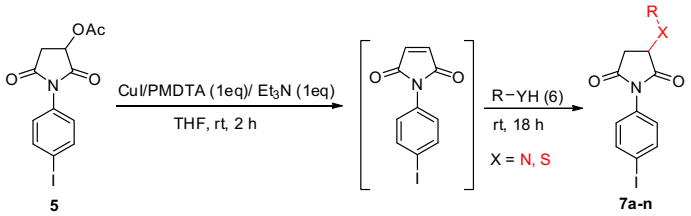
The pyrrolidine-2,5-dione **7n** (Table 2, entry 14) was converted into the corresponding sulfoxide (**11**) and sulfone (**12**) by only modulating the stoichiometry of the hydrogen peroxide in the presence of ammonium molybdate[51] with yields of 63% and 85%, respectively (Scheme 3).

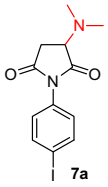
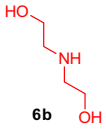
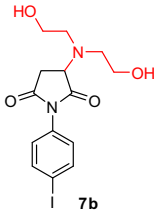
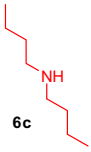
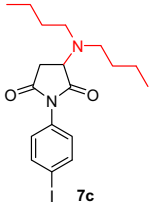
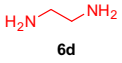
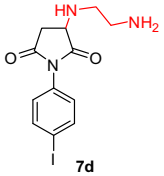
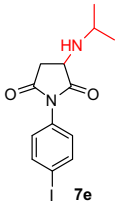
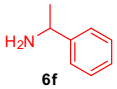
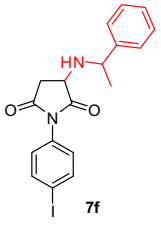
To show the versatility of the pyrrolidine-2,5-diones, acetylenic compound **7k** (Table 2, entry 11) was submitted to functionalization of the terminal triple bond using *n*-bromo butane and allyl bromide,[52] with the same conditions for both reactions. In both cases, the C-alkylated [(**13**) and (**14**)] and N-alkylated [(**15**) and (**16**)] products were formed in an almost 2:1 ratio; the yields are shown in Scheme 4.

Conclusion

In conclusion, we have presented a simple methodology to synthesize 4-substituted 1-(4-iodophenyl)pyrrolidine-2,5-dione derivatives under mild conditions in moderate-to-good yields. Also, 4-substituted 1-(4-iodophenyl)pyrrolidine-2,5-dione derivatives were converted in a one-pot, three-step reaction to

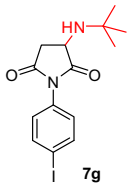
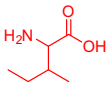
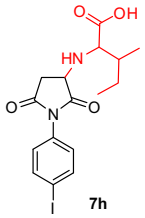
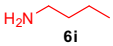
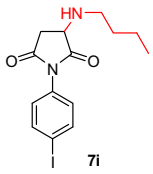
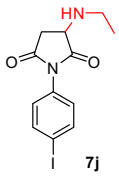
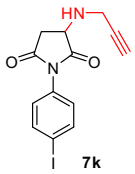
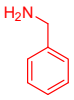
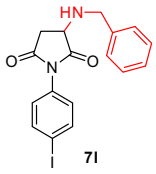
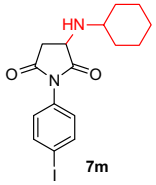
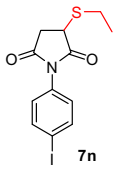
Table 2
Synthesis of pyrrolidine-2,5-dione derivatives



Entry	Amines	Product	Yield (%)[a]
1	 **6a**	 **7a**	70
2	 **6b**	 **7b**	nr
3	 **6c**	 **7c**	65
4	 **6d**	 **7d**	58
5	 **6e**	 **7e**	75
6	 **6f**	 **7f**	68

(*continued on next page*)

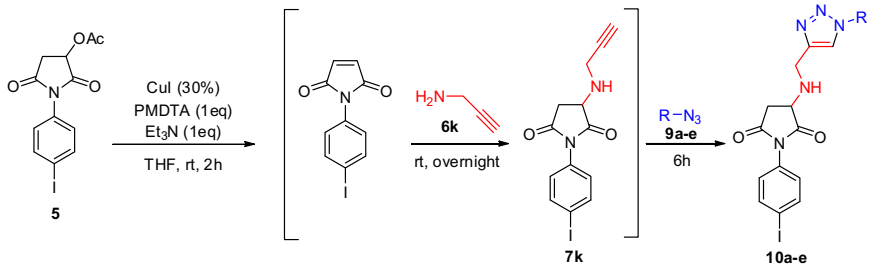
Table 2 (*continued*)

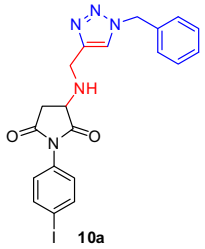
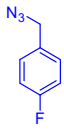
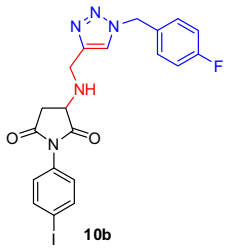
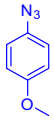
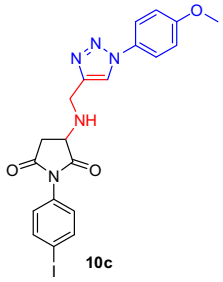
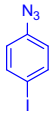
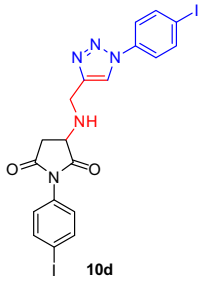
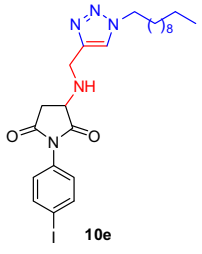
Entry	Amines	Product	Yield (%)[a]
7	 **6g**	 **7g**	66
8	 **6h**	 **7h**	nr
9	 **6i**	 **7i**	80
10	 **6j**	 **7j**	78
11	 **6k**	 **7k**	78
12	 **6l**	 **7l**	88
13	 **6m**	 **7m**	83
14	 **6n**	 **7n**	86

[a] Isolated yields.

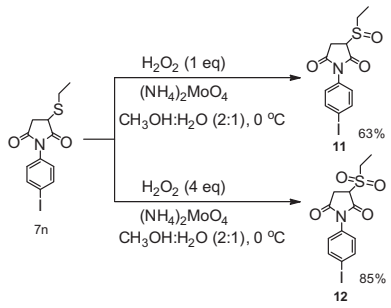
1,4-triazolyl derivatives through the 1,3-cycloaddition reaction catalyzed by CuI salt. The versatility of these compounds has been shown by the oxidation of a sulfur derivative to the corresponding sulfoxide and sulfone as well as the alkylation and allylation of a terminal acetylenic derivative. These transformations render this methodology a promising alternative route to access 4-substituted 1-(4-iodophenyl)pyrrolidine-2,5-dione derivatives with wide structural diversity.

Table 3
Synthesis of 1,4-triazole pyrrolidine-2,5-dione derivatives

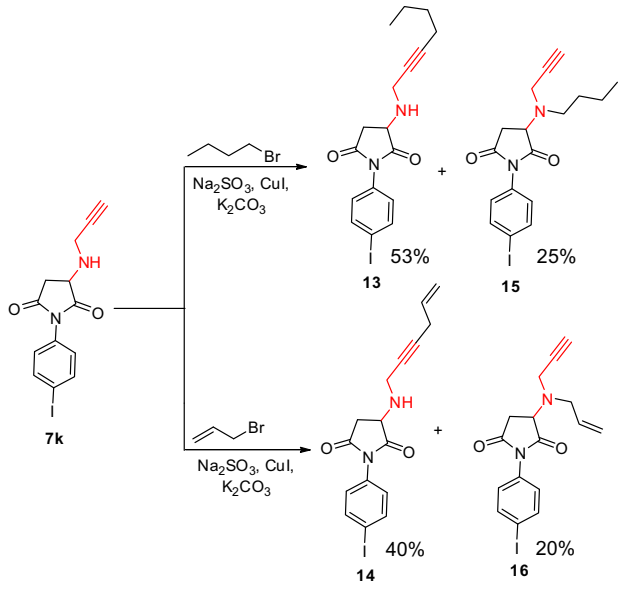


Entry	Azides	Product	Yield(%)[a]
1	 **9a**	 **10a**	73
2	 **9b**	 **10b**	75
3	 **9c**	 **10c**	77
4	 **9d**	 **10d**	53
5	 **9e**	 **10e**	68

[a] Isolated yields.



Scheme 3. Synthesis of sulfoxide (**11**) and sulfone (**12**).



Scheme 4. Alkylation and allylation of compound **7k**.

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Supplementary data

Supplementary data (experimental details and analytical data for all new compounds, including ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.066.

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49. *General procedure*: CuI (30%) was added to 3-(benzylamino)-1-(iodophenyl)pyrrolidine-2,5-dione (**7l**) in a solution of **5** (0.5 mmol) in dry THF (3 mL), followed by drop-wise addition of PMDETA (0.5 mmol) at room temperature. Et_3N (0.5 mmol) was then added and left stirring for almost 2 h, followed by drop-wise addition of amine **6** (0.5 mmol) to the solution and left stirring overnight. The reaction mixture was then evaporated, neutralized with 0.1 N HCl solution, extracted with ethyl acetate, and the organic phase was then washed with brine. The organic phase was dried over anhydrous Na_2SO_4,

filtered, and then evaporated under reduced pressure. The crude product **7l** was purified by column chromatography over silica gel using ethyl acetate/hexane (1:9). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.30 (br s, NH), 2.62 (dd, J = 18.08, 5.09 Hz, 1H), 2.93 (dd, J = 18.08, 8.48 Hz, 1H), 3.77–3.78 (m, 3H), 6.96–7.04 (m, 2H), 7.23–7.35 (m, 5H), 7.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 36.54, 51.89, 55.51, 94.11, 127.72, 127.96 (2C), 128.36, 128.77(3C), 131.31, 138.36 (3C), 173.68, 176.44. HRMS calcd for $C_{17}H_{16}IN_2O_2$ $(M+H)^+$: 407.0178; found: 407.0147.

50. *General procedure*: 1-(iodophenyl)-3-(((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)amino)pyrrolidine-2,5-dione (**10c**): CuI (30%) was added to a solution of **5** (0.5 mmol) in dry THF (3 ml), followed by drop-wise addition of PMDETA (0.5 mmol) at room temperature. Et_3N (0.5 mmol) was then added and left stirring for almost 2 h, followed by drop-wise addition of amine **6** (0.5 mmol) to the solution and left stirring overnight. Azide **9c** (1.3 equiv) was added to the stirring solution and stirred for about 2 h. Then, the solution was evaporated, 0.1 N HCl solution was added, extracted with ethyl acetate, and then the extract was washed with brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The crude product **10c** was purified by column chromatography over silica gel using ethyl acetate/hexane (1:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.73–2.85 (m, 2H), 3.34 (s, 3H), 3.89 (s, 2H), 5.35 (dd, J = 8.95, 4.43 Hz, 1H), 7.38–7.49 (m, 4H), 7.61–7.71 (m, 4H), 8.59 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 32.19, 50.40, 55.90, 69.84, 99.86, 111.91, 121.34 (2C), 127.96, 130.26, 130.40, 132.84, 132.98, 134.84, 137.35 (2C), 138.71, 158.93, 167.19, 169.57. HRMS calcd for $C_{20}H_{19}IN_5O_3$ $(M+H)^+$: 504.0454; found: 504.0398.
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