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Facile preparation of fused ring azolylureas

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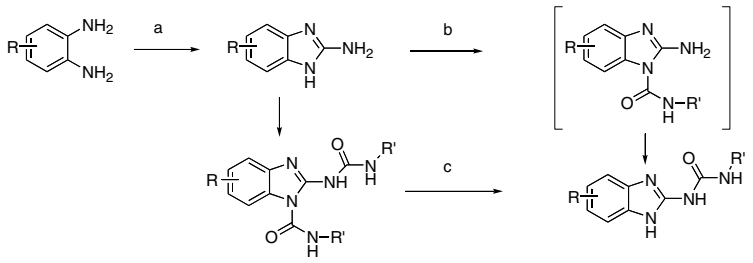
Abstract—Two novel reagents for the preparation of fused ring azolylureas are presented.

Exocyclic N-acylated aminobenzimidazoles have been of interest for several years due to their biological activity, for example, carbendazim (antifungal).[1] Thus, reagents for the one-step formation of 2-aminobenzimidazole carbamates from *o*-phenylenediamines are well known in the literature,[1–6] and are usually derived from either cyanamide or *S*-methylthiopseudothiourea. During the course of our work preparing inhibitors of bacterial topoisomerases, our initial approach for the synthesis of exocyclic ureas on the 2-aminobenzimidazole core followed literature precedents that presented several limitations.[7–10] This approach consisted of the reaction of the appropriate *o*-phenylenediamine with cyanogen bromide followed by acylation with an isocyanate and subsequent rearrangement to the *exo* position (Scheme 1). In some cases, it was convenient to make the bis-acylated adduct and then remove the *endo*-acyl group with ammonia. The acylations and rearrangements required a wide variety of reaction times, and in some instances the rearrangements did not occur. Diacylation required use of excess isocyanate, which led at times to diminished yields due to functional group incompatibility and/or cleavage of the urea portion of the molecule under the ammonia conditions used to remove the *endo*-acyl group.

Our interest in a one-pot procedure led us to examine potential cyanamide and thioallophanate-based reagents. With the exception of phenylureidocyanamide, very little information is available for the preparation of ureidocyanamide **3** reagents,[11–16] and no literature was found describing the preparation or the use of alkylureidocyanamides[17–22] or bis-ureido-*S*-methylthiopseudothioureas **4** for the direct transformation of *o*-aromatic diamines to fused-ring imidazoles or related heterocyclic systems.



Scheme 1. Reagents and conditions: (a) Br–CN, TEA, THF, CH_3OH, H_2O; (b) R′-NCO, THF; (c) 7 N NH_3, CH_3OH.

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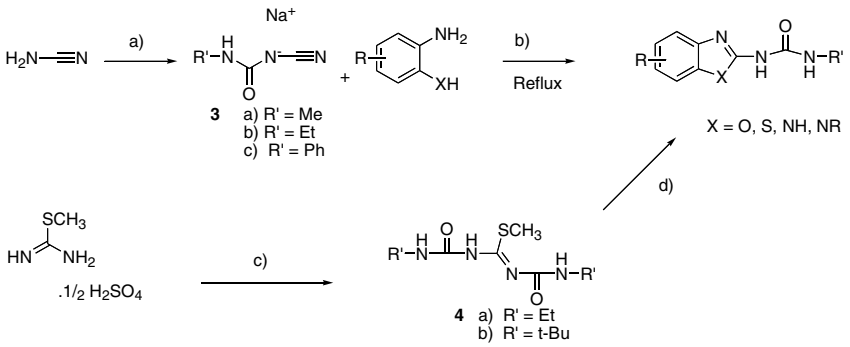


Scheme 2. Reagents and conditions: (a) R′-NCO, NaOH; (b) pH 3.5 buffer, reflux; (c) 2 equiv R′-NCO, TEA, CH_3CN or NaOH; (d) pH 3.5 buffer, reflux.

We report here the preparations of two distinct reagents derived from cyanamide and from *S*-methylthiopseudothiourea and the use of these to form fused-ring heterocyclic ureas (Scheme 2).[23] The cyanamide reagents **3** were readily prepared from the reactions of lower alkyl- or phenylisocyanates with excess cyanamide under alkaline conditions. The sodium salts of these compounds show stabilities of over one month in strongly alkaline aqueous solutions.[†] These salts can also be prepared and isolated as stable solids under non-aqueous conditions. Similarly, bis-alkylureido-*S*-methiopseudothioureas **4** yielded isolable solids.[‡]

As a class, the formation of the bis-acylated thiomethylpseudothioureas was limited to simple and branched-chain alkylisocyanate adducts. The reaction failed to react cleanly with phenylisocyanate. In contrast, the cyanamide reagents **3** formed with all isocyanates.

Reactions were generally carried out in aqueous buffered media. It was advantageous to add a small amount of 1,4-dioxane as a co-solvent to assist with the solubilization of the starting materials.[§]

During the reaction to form the benzimidazoles (heterocycles) from **3**, the pH of the medium increases as ammonia is liberated. Use of an aqueous buffer at pH 3.5 was found beneficial in keeping the reaction medium acidic. At a pH above 4.5, the reaction rate slowed or stopped. The buffered reaction solvent was sufficient when reagents **4** were used. In most instances, the desired heterocyclic urea precipitated as the reaction progressed. Elevating the pH of the reaction mixture with bicarbonate prior to filtration often produced additional amounts of the desired product. A simple water–methanol wash usually gave pure materials. The yields of the azolylureas were often higher using reagents **4** (Table 1).

These reagents were also useful in preparing other fused ring system ureas, as well. Reaction with *o*-aminophenols and *o*-aminothiophenols gave the corresponding benzoxazoleureas (Table 1, compounds **9** and **10**) and benzothiazoleureas (Table 1, compound **11**), respectively; similarly reactions with *o*-diamino pyridines and pyrimidines gave the corresponding imidazopyridineureas (Table 1, compound **19**) and imidazopyrimidineureas (Table 1, compound **21**) (Scheme 3).

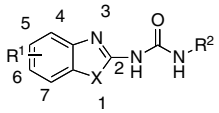
In conclusion, we have described two new reagents and methods for their use to make fused ring azoles. These

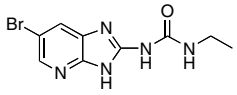
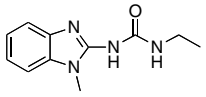
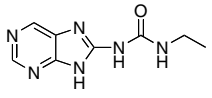
[†] It was convenient to prepare stock solutions of both reagents. Reagents **4** were dissolved in dioxane (although they could be used as a solid); likewise a 0.8 M aqueous solution was made for the cyanamide reagents **3**.
Preparation of sodium *N*-ethylureidocyanamide: 1.68 g (0.04 mol) of cyanamide was dissolved in 10 ml 1.5 M sodium hydroxide followed by dropwise addition of 0.8 ml (0.01 mol) ethylisocyanate. After stirring for 30 min at room temperature, 5 ml of 3.0 M sodium hydroxide was added, and again followed by dropwise addition of 0.8 ml (0.01 mol) of ethylisocyanate. The resulting solution was stirred for 30 min. HPLC (10-90-8 gradient, reverse phase, 98.9%water–1%acetonitrile–0.1%TFA/99.9%acetonitrile–0.1%TFA) gave a characteristic retention time of 3.7 min (214 nm).

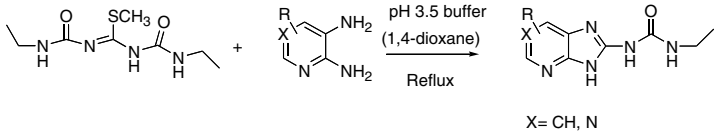
[‡] *Preparation of S-methyl N-t-butyl-carbamoyl-4-t-butylthioallophanimidate*. Triethylamine (30 ml, 0.215 mol) was added to a suspension of 2-methylthiopseudothiourea hemisulfate (10 g, 0.0718 mol) in acetonitrile (72 ml). *t*-Butylisocyanate (25.6 ml, 0. 215 mol) was added dropwise over 30 min with stirring. The thick white mixture was stirred at room temperature for 40 h, then water was added (50 ml). The biphasic mixture was extracted with ethyl acetate (2 × 150 ml). The combined organic extracts were washed with water (100 ml), dried over magnesium sulfate and concentrated in vacuo to give 24.3 g of white solid. This was recrystallized from hot methanol/water to give 17 g of the desired bis-acylated material as a white solid (82% yield).

[§] *General Procedure for the preparation of the urea derivatives using S-methyl N-alkyl carbamoyl-4-alkylthioallophanimidate*. A round bottom flask equipped with a reflux condenser was charged with a diamine (2.0 mmol), *S*-methyl *N*-alkyl carbamoyl-4-alkylthioallophanimidate **4** (2.4 mmol, 1.2 equiv), and dioxane (2 ml). The mixture was then diluted with aqueous buffer, pH 3.5 (sodium acetate trihydrate/1 N aqueous sulfuric acid, 18 ml), heated to 95–100 °C and stirred at that temperature for 10 min to 60 h (monitored by HPLC and LCMS). The resulting mixture was cooled to room temperature, slowly basified to pH 7–8 with saturated aqueous $KHCO_3$ and diluted with water. The precipitate was then isolated by filtration and washed with 30% MeOH in water, and EtOAc in succession, and dried in vacuo. The resulting desired ureas are essentially pure by HPLC and ^1H NMR (⩾97% pure), however, if necessary, these can be further purified by flash chromatography (Isco CombiFlash® Companion). The analogous procedure was followed when the cyanamide reagents were used instead of the methylthioallophanates. Ethanol, THF and DMSO were also used successfully as co-solvents.

Table 1. Reactants, products, reaction times and melting points



Entry	R^1	R^2	X	Time (h)	Yield (%) [Reagent **3** or **4**]	Mp (°C)
1	5-Cl	Et	NH	1	96 [4]	330–332
2	5-CO_2H	Et	NH	1	99 [4]	298–299
3	5-CO_2CH_3	ET	NH	0.16	93 [4] 65 [3]	303–304
4	4-OH	Et	NH	1	77 [4]	228–229
5	4-Me	Et	NH	1.25	85 [4]	320–323
6	5-NO_2	Et	NH	0.25	98 [4]	>350
7	5-Br, 6,7-Me	Et	NH	20	64 [3]	>245
8	5-Br	Et	NH	20	89 [3]	>260
9	H	Et	O	2	60 [4]	166–167
10	5-CO_2CH_3	Et	O	60	79 [4]	165
11	H	Et	S	1	73 [4]	199 dec
12	H	Et	NH	1	98 [4]	259–260
13	5-OMe	Et	NH	1	99 [4]	350–353 dec
14	7-NO_2	Et	NH	1	80 [4]	>350
15	5-F	Et	NH	1	94 [4]	166–167
16	H	Ph	NH	2.25	48 [3]	332–333
17	5-Me	*t*-Bu	NH	1	63 [4]	330–331 dec
18	7-NO_2	Me	NH	6	43 [3]	213–316 dec
19				1	57 [4]	312–314
20				1.25	91 [4]	163–165
21				2.75	68 [4]	290–292



Scheme 3.

reactions are convenient to run and have been used on scales greater than 100 g (data not shown).

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