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The Preparation of 2,4-Disubstituted Thiazoles on Solid Support

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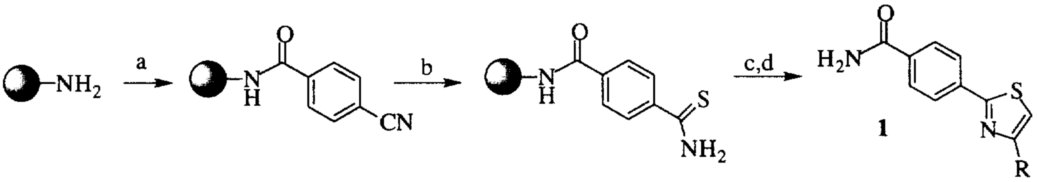
Abstract: Conversion of a nitrile to a thioamide on solid support has been achieved. This permits an efficient synthesis of 2,4-disubstituted thiazoles.

Recently Flygare and co-workers reported a Hantzch thiazole synthesis starting from a thiourea bound to a solid support.[1] Here we report some of our results using a resin-bound thioamide. We envisioned that a nitrile could be converted to a thioamide while attached to a solid support. Subsequent reaction with an α-halo ketone would give the thiazole. This scheme appealed to us since there are many readily available bifunctional building blocks containing the nitrile group. The second functional group is used for resin attachment. A specific embodiment of this idea is shown in Scheme 1.



Scheme 1. Conditions: a) 4-Cyanobenzoic acid, PyBOP, NMM, NMP b) Dithiophosphoric acid O,O-diethylester, THF, H_2O, 70° C c) alpha-halo ketone (0.5 M in DMF), 70°C d) 95/5 TFA/H_2O

Standard peptide coupling reagents were used to load 4-cyanobenzoic acid onto Rink amide resin. Conversion to the thioamide was achieved by heating the resin with dithiophosphoric acid O,O-diethyl ester in a mixture of THF and water.[2] The conversion of nitrile to thioamide was monitored by cleavage of an aliquot of resin, followed by hplc. In this particular instance the retention time of the starting 4-cyanobenzamide was 11.94 min[3] while the product thioamide had a retention time of 10.10 min. Reactions with greater than 300 mg of resin were allowed to go overnight and then monitored before proceeding to the next step. If incomplete the sulfurization reaction was repeated. The bright yellow thioamide containing resin was dried in vacuo. It was then reacted with the α-halo carbonyl compound at 70°C in DMF overnight. For some acyclic α-bromo ketones the required time is probably much shorter, however, for cyclic α-bromo ketones the longer time was necessary.

Four examples of thiazoles synthesized by this route are given in Table 1. The examples were chosen to feature interesting cyclic or heterocyclic α-bromo ketones (**1a**,**b** and **d**) or an α-chloro ketone (**1c**). For

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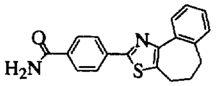
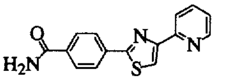
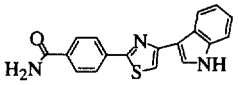
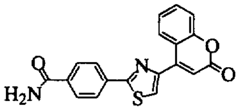
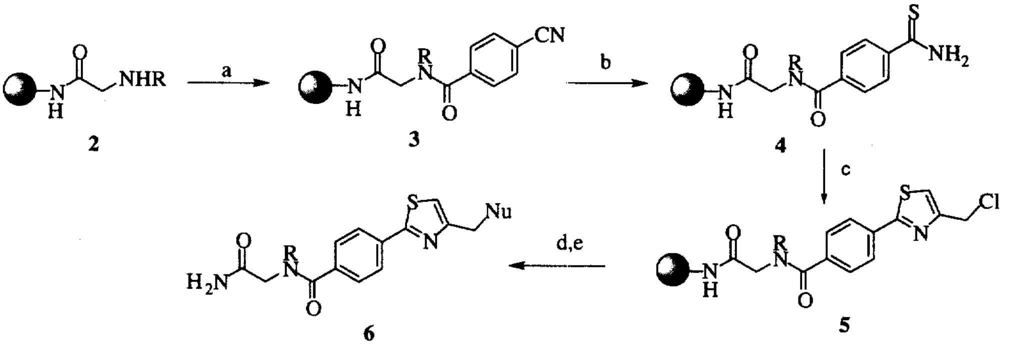
comparison, one reaction was also performed in 1,4-dioxane (RT, overnight) since this solvent was recommended for the formation of thiazoles from thioureas.[1] These conditions also produced **1b**, albeit in slightly lower purity (65 %, hplc). Yields ranged from modest to good, but purities were excellent as judged by hplc (254 and 214 nm) as well as ^{1}H nmr. The major impurity appeared to be a small amount of 4-cyanobenzamide seen in several cases.

Table 1

		Purity	Yield	MS(M+1)
1a		84	97	321
1b		98	50	282
1c		90	74	320
1d		95	34	349

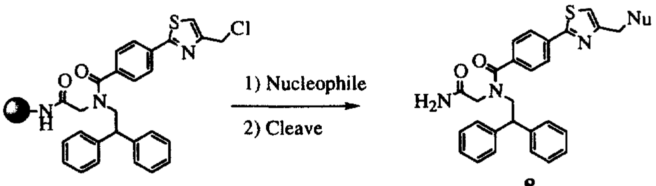
There are many possible variants of this resin based thiazole synthesis. Scheme 2 shows a peptoid based approach to introduce two points of diversity.



Scheme 2. a) 4-Cyanobenzoic acid, DIC, DMF, o.n. b) Dithiophosphoric acid O,O-diethyl ester, THF/H_2O, 70°C, o.n. c) 1,3-Dichloroacetone, DMF, 70°C, 4 h d) Nu= amine, phenol, thiol, NMP, 70°C, o.n. e) 95/5 TFA/ H_2O, 20 min., RT

Intermediate **2** was constructed on Rink amide resin using standard peptoid synthesis conditions.[4] Coupling with 4-cyanobenzoic acid and thioamide formation gave **4**. Reaction with 1,3 dichloroacetone[5] (70°C, 4h) gave highly useful resin bound chloromethyl thiazole **5**. The chloromethyl group was then substituted with a variety of amine, thiol and phenolic nucleophiles. These substitution reactions were performed at 70°C in NMP, with added cesium carbonate in the case of the thiols and phenols. Examples of each class of nucleophile are shown in Table 2.

Table 2



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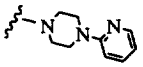
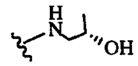
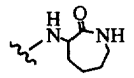
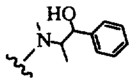
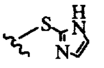
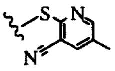
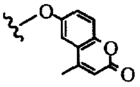
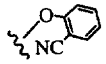
Compound	Nucleophile	HPLC(min)	HPLC Purity	MS (M+1)	Yield (%)
8a		24.07	98	617	58
8b		21.92	98	529	81
8c		22.54	98	582	90
8d		25.84	98	619	95
8e		22.90	98	554	88
8f		34.61	98	604	74
8g		32.78	98	630	70
8h		32.81	98	573	63

Table 2 shows representative reactions from a much larger set of nucleophiles which has been validated for library synthesis. In each case the final product after lyophilization was > 98% pure as judged by hplc (absorption at 254 nm) and the yields were quite acceptable. All products gave the expected protonated parent ion by ion-spray mass spectrometry. The ^{1}H nmr spectra of several of the compounds are complex since cis-trans rotamers are present at the tertiary amide. However, the spectra are consistent with the assigned structures.

The synthesis shown in Scheme 2 is useful for the production of a combinatorial library. If the nucleophile is a primary amine, the synthesis can be extended by capping the amine with an acid, acid chloride, isocyanate, sulfonyl halide, FMOC-amino acid and so on. As previously mentioned, the large number of bifunctional nitrile containing building blocks offers many possible variations on this simple, but useful, resin based Hantzch thiazole synthesis. [6,7]

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References and Notes

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1. Kearney, P.C.; Fernandez, M.; Flygare, J.A. *J. Org. Chem.* **1998**, *63*, 196-200.
2. Shabana, R.; Meyer, H.J.; Lawesson, S.O. *Phosphorous and Sulfur* **1985**, *25*, 297-305.
3. HPLC was performed on a Waters Millenium system using an Alltech Alltima C-18 reversed phase column 4.6 x 250 mm. The flow rate was 1.0 ml/min, injection volume 2-10μl. The linear gradient used was 5% acetonitrile to 81% acetonitrile in water over 36 min, then increasing to 100% acetonitrile over 4 min. Both solvents contained 0.1% TFA by volume. UV detection was at 220 and 254 nm.
4. Zuckermann, R.N.; Kerr, J.M; Kent, S.B.; Moos, W.H. *J. Amer. Chem. Soc.* **1992**, 114, 10646-10647.
5. Marzoni, G. *J. Heterocyclic Chem.* **1986**, *23*, 577-580.
6. Typical Experimental Procedure (Compound **8a**) : Rink amide resin (NovaBiochem, San Diego, CA, 0.57 mMol/gm loading, 3.0 gm) was deprotected with 20% piperidine in DMF (40 mL) for 0.5 h at RT. The resin was washed 3x with DMF and 4x with dichloromethane (DCM). The resin was then treated with a solution of bromoacetic acid (3.0 gm, 21 mMol) in DMF (30 mL) followed by diisopropylcarbodiimide (DIC) (3.0 mL). After 0.5 h agitation at RT the solvent was removed and the coupling repeated. The resin was washed 3x with DMF and 4x with DCM. Treatment with a 1M solution of 2,2-diphenylethylamine in DMSO (20 mL) at RT for 2h gave intermediate **2a**. The resin was washed 3x with DMF and 4x with DCM. The resin was then treated with a solution of 4-cyanobenzoic acid (17 mMol) and DIC (17 mMol) in DMF (25 mL) for 4h at RT with shaking. The resin was washed as before and then dried overnight in vacuo at RT. The dried resin (1.5 gm) was placed in a 20 mL glass scintillation vial and treated with THF (13 mL), dithiophosphoric acid O,O-diethyl ester (3.15 mL, 20 mMol, obtained from TCI America, Portland, Ore) and water (3.15 mL). The reaction was then heated overnight at 70°C (**Caution:** pressure develops during this reaction. Therefore the mixture should be kept in the hood behind a shield. Temperatures greater than 75°C are not recommended. The use of a larger sized vial or reduction of the volumes from those given above may be advisable. The vial must be cooled to RT before opening).The resin was washed well with DMF, water, DMF and then dichloromethane and then dried in vacuo. The resin bound thioamide is normally bright yellow in color. The dried resin (1.5 gm) was treated with DMF (10 mL) and then 1,3-dichloroacetone (0.64 gm, 5 mMol), followed by heating for 4h at 70°C. The resin was washed 3x with DMF and 4x with dichloromethane, then dried in vacuo at RT. The resulting resin **5a** could be stored for several months in the dark without apparent deterioration. **5a** (100 mg) was placed in an 8 mL vial and treated with NMP (2 mL) and 1-(2-pyridyl)piperazine (0.30 mL) followed by heating overnight at 70°C. The resin was well washed with DMF and dichloromethane and then cleaved with 95/5 TFA/H_2O for 20 min. The resin was filtered off and washed with dichloromethane. The filtrate was concentrated in vacuo and lyophilized from acetonitrile/water to give **8a.**
7. Commercially available bifunctional nitriles include 3- and 4-cyanobenzenesulfonyl chloride, 3- and 4-cyanophenyl isocyanate, 3- and 4-cyanophenol as well as the 3- and 4-cyanobenzoic acids and the corresponding acid chlorides. Other useful building blocks such as the 3- or 4-cyanobenzylamines can be prepared from the commercially availablebenzyl halides.