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Resin-bound thiophenols as S_NAR-labile linkers: application to the solid phase synthesis of aminopyridazines

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Abstract

A versatile approach for the solid phase synthesis of aminopyridazines was developed. Commercially available or novel resin-bound thiophenols are used to link 3,6-dichloropyridazine to solid supports and to introduce diversity into the molecule by direct cleavage of nucleophilic amines without oxidation to sulfones. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Constructing libraries by solid phase synthesis of nonpolymeric small organic molecules has been the recent focus of combinatorial chemistry.[1] Many pharmacologically important molecules such as benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, β-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, oxazolones, etc., have been prepared on solid support in the last few years.[2]

Aminopyridazines constitute an important pharmacophoric moiety present in many drugs acting on various pharmacological targets. Especially, the aminopyridazine nucleus is found in dopaminergic, serotoninergic, cholinergic and GABA-ergic ligands, as well as in monoamine oxidase and acetylcholine esterase inhibitors.[3] Therefore, we found it of prime importance to design and develop a solid phase chemistry giving access to a wide variety of aminopyridazine analogs.

To our knowledge, the solid phase synthesis of pyridazines has never been reported. Conventional strategies usually require an attachment point from the template to the resin which remains after the cleavage and limits the versatility of the approach. Therefore, we wanted to develop traceless linkers or linkers that would provide an additional point of diversity upon cleavage. In this context, we were interested in transposing to pyridazines the method developed for aminopyrimidines by Obrecht et al. and Gayo and Suto, and which involves a nucleophilic displacement of the 2-benzyl sulfonyl group of pyrimidines by amines as cleavage reaction.[4,5]

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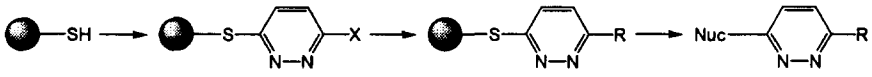
We reasoned that thiol linkers would combine the advantage of a relatively inert sulfide linkage[4] with an easy nucleophilic displacement of the thiolate ion at the last step of the synthesis, allowing access to a wide range of disubstituted pyridazines, according to the general Scheme 1.

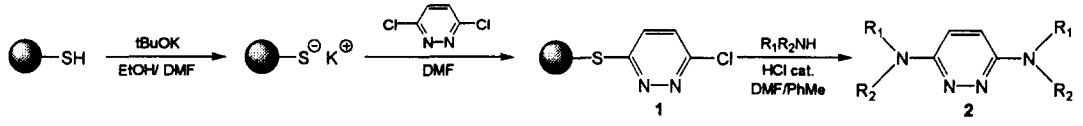


Scheme 1.

Thiophenol linkers might represent an interesting alternative to benzyl sulfones, for nucleophilic substitution/cleavage of heterocycles in general, and of pyridazines in particular. Therefore, prior to embarking on a full library synthesis program, we studied several polymeric thiol supports as pyridazine linkers and optimized their nucleophilic substitution (cleavage) by *n*-butylamine.

Two commercially available thio resins have been used: the PS-*meta*-thiophenol resin,[6] which is usually used as a scavenger rather than as a support for solid phase synthesis, and the TG-benzylthiol resin,[4] to try a PEG-grafted polystyrene resin. To complete our study, we prepared three additional thio resins: the PS-thiobenzyl resin, for comparison with the published studies;[4,5] the 3-thiopropyl ether, an aliphatic derivative of the PS-thiobenzyl resin; and the PS-*para*-thiophenol resin,[7] for comparison with commercially available PS-*meta*-thiophenol resin.[6]

The different thio resins, except the *para*-benzylthiol TG resin (**1d**),[4,8] were converted into the corresponding thiolates with potassium tertiobutylate in DMF/EtOH at room temperature for 1 h. Reaction with 3,6-dichloropyridazine was performed to afford the thio resin-linked pyridazines as shown in Scheme 2.[9]



Scheme 2.

Direct nucleophilic cleavage by *n*-butylamine in DMF:toluene (1:1) at 100°C was studied as a function of time in the presence of catalytic amounts of HCl in order to accelerate the nucleophilic displacement, the protonated heterocycle being more reactive than the neutral heterocycle.[10] For comparison purposes, the thiophenyl and thiobenzyl linkers were oxidized to the corresponding sulfones as previously described[4,5] and their nucleophilic cleavage by *n*-butylamine was also studied.[11] Results are given in Table 1.

We found that the PS-thiophenol linkers, especially the PS-*para*-thiophenol,[7] are more reactive S_NAR leaving groups than benzylthiol linkers (Table 1). This reactivity is of particular interest since 3-halopyridazines are known to be less reactive than 2-halopyrimidines to nucleophilic displacement. Moreover, for instance, nucleophilic substitutions of 3-methylsulfonylpyridazines in solution required more drastic conditions (pressure, longer time).[12]

On the other hand, these thiophenol resins do not need to be activated by oxidation before being displaced by nucleophilic amines, ruling out the possibility of an oxidative attack elsewhere on the scaffold (e.g. a pyridazine *N*-oxidation[13]). However, the cleavage conditions of the thiophenyl linker are sufficiently strong (24–48 h, 90°C) to provide enough chemical stability to this anchoring mode towards many reaction conditions. As such, our procedure is an interesting alternative in the sulfur linker family, particularly since it represents a 'traceless linker' methodology rather than a 'safety-catch linker' methodology.

To evaluate the scope and limitations of our approach, we treated the commercially available PS-*meta*-thiophenol resin[6] with a structurally diverse set of amines (Table 2). A catalytic amount of HCl and 5

Table 1

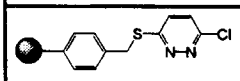
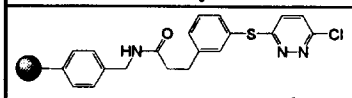
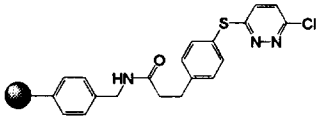
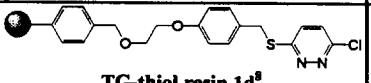
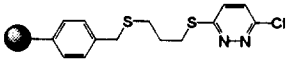
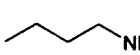
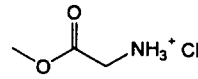
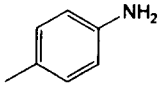
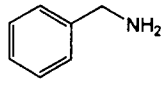
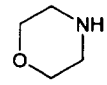
Resins	Yield[14] of 2 (R_1=H, R_2=n-butyl)						
	without oxidation of the resin				after oxidation of the resin[4,5]		
	24 h	48 h	72 h	96 h	24 h	48 h	96 h
 PS-thiobenzyl resin 1a	0%	0%		25%	20%	35%	50%
 PS-*meta*-thiophenol 1b[6]	55%	80%	**100%**		90%	**100%**	
 PS-*para*-thiophenol resin 1c[7]	**90%**	**100%**			95%	**100%**	
 TG-thiol resin 1d[8]			20%			40%	
 PS-propanethiol resin 1e			90%				

Table 2

R_1R_2NH				
Yield[14] of 2	100 %	90 %	65%	
R_1R_2NH				
Yield[14] of 2	50 %	100 %	75 %	90 %

equiv. of amines were required for the cleavage step.[11] The excess of reagent was easily eliminated by a water washing and we obtained the pure final disubstituted product (purity ≥95% as indicated by NMR) by precipitation in diethylether.[14]

In summary, our findings represent the first approach to the solid phase synthesis of pyridazines. In comparison to other heterocycle syntheses on thio resins, the strategy presented does not involve an additional oxidative step that could damage the scaffold. We found that the *para*-thiophenol linker represents the most suitable and versatile leaving group for the preparation of original substituted pyridazines.[15]

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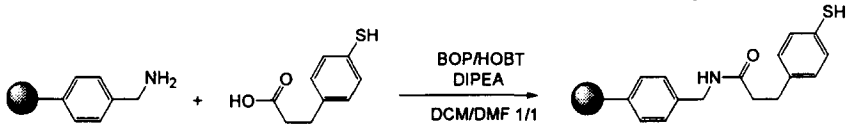
7. We have synthesized the PS-*para*-thiophenol resin starting from an aminomethylated polystyrene resin.



8. Preparation of polymer-bound chloropyridazine **1d**: To 1 equiv. of Novasyn® TG thiol resin swelled in DMF were added 5 equiv. of 3,6-dichloropyridazine followed by 5 equiv. of triethylamine. After shaking 12 h, the solution was removed by filtration and the resin was washed with three cycles of DMF, DCM, MeOH, DCM, and dried. The infrared spectrum of the resin included pyridazine absorptions at 1139 cm^{-1} and 1382 cm^{-1}.
9. General procedure for the preparation of polymer-bound chloropyridazine **1**: To the sulfur resin swelled with DMF and gently stirred, a deoxygenated solution of 1.5 equiv. of *t*BuOK in a minimum amount of EtOH was added under argon. The mixture was stirred at room temperature. After 1 h, the mixture was treated with 10 equiv. of 3,6-dichloropyridazine and allowed to react for 24 h. The solution was removed by filtration and the resin was washed with three cycles of DMF, DCM, MeOH, DCM, and dried. The infrared spectrum of the resin showed pyridazine absorptions at 1139 cm^{-1} and 1382 cm^{-1} and disappearance of the -SH absorption at 2560 cm^{-1}.
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11. General procedure for the cleavage of polymer-bound chloropyridazines: To a sulfur resin swelled in DMF:toluene 1:1 and gently stirred, 5 equiv. of amine and a catalytic amount of HCl were added under argon. The solution was allowed to react for 24 h, 48 h, or 72 h at 90°C. Then the solution was removed by filtration and the resin was washed with three cycles of DMF, toluene, DCM, MeOH, DCM, and dried. The infrared spectrum of the resin showed the partial or total disappearance of pyridazine absorptions at 1139 cm^{-1} and 1382 cm^{-1}.
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14. Yields of **2** have been determined as follows: Cleavage is followed by IR (partial or total disappearance of pyridazine absorption bands) and the amount of **2** recovered is measured by weighing (more than 300 mg of resin per experiment is used). The yield is deduced, based on the theoretical loading of commercial resin.
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