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Solid-phase combinatorial synthesis of 5-arylalkylidene rhodanine

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Abstract

Rhodanine-3-acetic acid was loaded on Wang resin or Rink amide resin. Alternatively, the thiocarbonyldiimidazole-activated Wang amino acid resin or 2-chlorotrityl resin was reacted with methyl thioglycolate to yield the rhodanine moieties. It was then condensed at the C-5 active methylene with either aromatic aldehydes or aromatic ketones. 5-Arylalkylidene rhodanine was obtained upon resin cleavage.

Keywords: solid-phase synthesis; rhodanine; aldehydes; ketones; condensation.

Solid-phase and solution-phase organic synthesis as applied to the assembly of chemical libraries is widely practiced in many academic and industrial laboratories throughout the world. Combinatorial chemistry is now regarded as an important component of the drug discovery process.[1]

Thiazolidinone derivatives are reported to have anticonvulsant,[2] antibacterial,[3] antiviral[4] and anti-diabetic properties.[5] For example, pioglitazone and rosiglitazone were launched recently for type II diabetes mellitus. The rhodanine (2-thioxo-4-thiazolidinone) moiety was synthesized by various methods such as the addition of isothiocyanate to mercaptoacetic acid followed by acid cyclization, or the reaction of ammonia or primary amines with carbon disulfide and chloroacetic acid in the presence of bases.[6] Knoevenagel condensation with aromatic aldehydes at the nucleophilic C-5 active methylene was accomplished using piperidinium benzoate in refluxing toluene[7] or sodium acetate in refluxing glacial acetic acid.[6] However, the acidic conditions are unsuitable for acid labile Rink amide, 2-chlorotrityl and Wang resin.

In this paper, we reported a simple and straightforward procedure using milder conditions for solid-phase combinatorial synthesis of 5-arylalkylidene rhodanine. Two synthetic routes were employed for the formation of rhodanine moieties on solid supports (Scheme 1). Rhodanine-3-acetic acid was independently coupled to Wang resin and Rink amide resin by standard conditions

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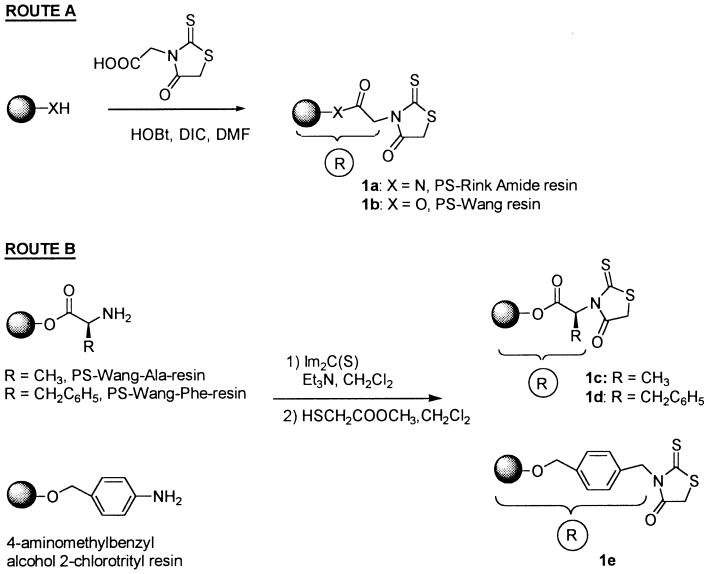
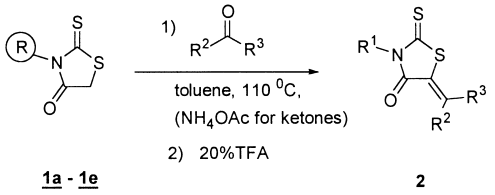


Scheme 1. Formation of rhodanine moieties on solid supports

to give **1a** and **1b**, respectively (Route A). For additional diversity, Fmoc-Ala-Wang resin, Fmoc-Phe-Wang resin and 4-aminomethylbenzyl alcohol 2-chlorotrityl resin were also employed to give **1c**, **1d** and **1e**, respectively (Route B).[8] Synthesis of these linkers involved the generation of thiourea by reacting thiocarbonyldiimidazole[9] with their respective amines. Displacement of imidazole by methyl thioglycolate followed by spontaneous cyclization gave the rhodanine moiety.

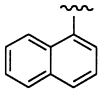
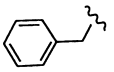
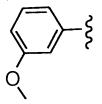
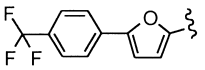
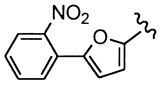
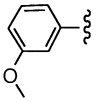
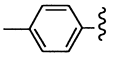
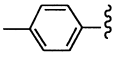
Knoevenagel condensation of the C-5 active methylene of rhodanine (**1a**–**e**) with aromatic aldehydes proceeded very smoothly to completion by heating only, whereas that with aromatic ketones proceeded only in the presence of ammonium acetate with heating (Scheme 2). Heating at a high temperature (110°C) was essential to ensure complete condensation. Toluene was therefore chosen as the solvent for its high boiling point and its good swelling property.



Scheme 2. Condensation of **1** with aldehydes and ketones

The cleaved 5-arylalkylidene rhodanines (**2**) were characterized by ^{1}H NMR and MS. Twelve representative examples were randomly selected and their crude yields and purities were summarized in Table 1. Condensation of the C-5 active methylene of rhodanine (**1a**–**e**) with aldehydes and ketones gave comparable yields. The yields of the final products were not affected by the bulkiness of aldehydes and ketones. Only the thermodynamically stable *Z*-isomer was obtained except in entry 4 which gave a 1:1 (*E*:*Z*) mixture.[10] The rhodanine formation and condensation

Table 1
The yield and HPLC purity of compound **2**

Entry	R^1	R^2	R^3	% Yield[a]	HPLC Purity[b]
1	CH_2CONH_2	CH_2CH_3		83	69
2	CH_2COOH	CH_3		78	77
3	CH_2COOH	CH_3		60	74
4	CH_2COOH	CH_2CH_3		85	91
5	CH_2COOH	$CH_2CH_2CH_3$		75	77
6	CH_2COOH	H		88	90
7	CH_2COOH	H		68, 72[c]	54
8	CH_2COOH	H		77	87
9	CH_2COOH	H		82	69
10	$CH(CH_3)COOH$	H		74[11]	56
11	$CH(CH_2C_6H_4)COOH$	H		71[11]	79
12	$CH_2C_6H_4CH_2OH$	H		81	74

[a]Crude yield calculated based on theoretical loading of the resins. [b]HPLC purity at 300 nm with a Hypersil ODS C18 reverse-phase column (2.1 x 200mm). [c]2 x 5 mol eq of *m*-anisaldehyde was used.

with carbonyl compounds worked equally well with Rink amide, Wang and 2-chlorotrityl resins as indicated by the isolated yields of compound **2**, which were above 60%. Their HPLC purities ranged from 54 to 90%. There was no significant increase in yield when the condensation reaction was repeated twice (entry 7).

This paper demonstrated the first solid-phase synthesis of 5-arylalkylidene rhodanine by Knoevenagel condensation of carbonyl compounds with the C-5 active methylene of rhodanine. The conditions employed were mild and the synthesis is applicable to both acid and base sensitive linkers. We are currently exploring the reaction using different resin linkers.

Acknowledgements

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8. Preparation of **1d**: To 370 mg of Fmoc-Phe-Wang resin (0.55 mmol/g, Novabiochem) were added 20% piperidine in DMF and the mixture shaken for 30 min. The resin was washed (DMF, MeOH and CH_2Cl_2) and dried under vacuum. A mixture of resin, thiocarbonyldiimidazole (5 mol equiv.) and triethylamine (3 mol equiv.) in CH_2Cl_2 was shaken for 1 h. The filtrate was drained away. The resin was swollen in CH_2Cl_2 and methyl thioglycolate (5 mol equiv.) was added. The reaction mixture was further shaken for 12 h. The resin was washed (DMF, MeOH and CH_2Cl_2) and dried. Preparation of **2**: The loaded resin (**1a**–**1b**) (200 mg), a ketone and ammonium acetate (5 mol equiv. each) were suspended in toluene (4 mL) and heated at 110°C for 3 days. In the case of aldehydes, the loaded resin (**1a**–**1e**) (200 mg) and an aldehyde (5 mol equiv.) was heated in toluene (4 mL) at 110°C for 12 h. The resin was washed (DMF, MeOH and CH_2Cl_2), resuspended in TFA:CH_2Cl_2 (20:80), and shaken for 1 h. The filtrate was pooled and concentrated to yield product **2**.
9. Munson, M. C.; Cook, A. W.; Josey, J. A.; Rao, C. *Tetrahedron Lett.* **1998**, *39*, 7223–7226. Thiocarbonyldiimidazole was used instead of carbonyldiimidazole.
10. The stereochemistry was determined according to Ref. 5a and b. It was reported that only the thermodynamically stable *Z*-isomer was observed for all arylidene rhodanines and the methylene proton of *Z*-isomer was more downfield (7.9 ppm) than that of the *E*-isomer (7.4 ppm) due to the interaction with the carbonyl group at the 4-position.
11. Racemization was determined by ^1H NMR using the chiral lanthanide shift reagent tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) as an additive in $CDCl_3$. We observed 75 and 100% of the *S*-configuration in the Ala- and Phe-derived products, respectively.