Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 2387–2391
Tetrahedron Letters

Traceless solid-phase synthesis of 2-amino-5-alkylidene-thiazol-4-ones

Maurizio Pulici* and Francesca Quartieri

Department of Chemistry, Nerviano Medical Sciences, Viale Pasteur 10, I-20014 Nerviano (MI), Italy

Received 5 January 2005; revised 10 February 2005; accepted 11 February 2005

Abstract—2-Amino-5-alkylidene-thiazol-4-ones bearing two diversity points are prepared by a solid-phase strategy exploiting rhodanine as the starting material. Rhodanine is first loaded on bromo-Wang resin, subjected to Knovenagel condensation with aldehydes, and cleaved off the resin in a traceless manner by means of an amine.

2-Amino-5-alkylidene-thiazol-4-one **1** (Fig. 1) represents one of the privileged scaffolds in drug discovery: this heterocyclic core is in fact found in more than 15,000 molecules synthesized so far, the biological activities of which have been reported in approximately 150 publications, including 80 patents.[1] A survey of the most recent papers dealing with the pharmacological properties of such compounds reveals that they may be useful for the treatment of cystic fibrosis,[2] as β-3 agonists (potentially applicable to the treatment of metabolic diseases[3]), as antibacterial,[4] antiviral,[5] cardiotonic,[6] and anti-inflammatory[7] agents. Among the latter, it is worth mentioning the case of Darbufelone mesilate®, reported to have reached Phase II clinical trials as a dual inhibitor of cellular prostaglandin and leukotriene production[7d].

Given this background, it is not surprising that a number of routes have been developed in order to target these compounds. The 2-amino-5-alkylidene-thiazol-4-one nucleus can be assembled directly using acyclic building blocks (Scheme 1) or can be attained by functionalization of the thiazolone core, in turn prepared using either acyclic or cyclic precursors (Scheme 2).

In the first case the synthetic process often involves a substituted thiourea, which can be cyclocondensed with an α,β-di halo carboxylic acid derivative (*Route A*)[8] or with an alkyl acetylenedicarboxylate (in this case R3 must be COOR, *Route B*)[9] The targeted compounds can also be achieved by a bromine-mediated oxidation of propenoylthioureas (*Route C*)[10] and by means of a three-component reaction where the thiourea is reacted

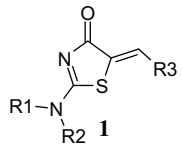
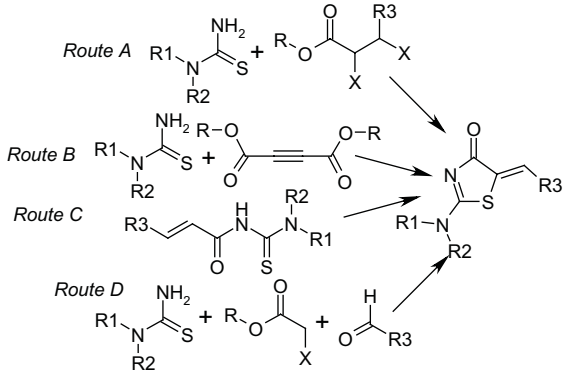


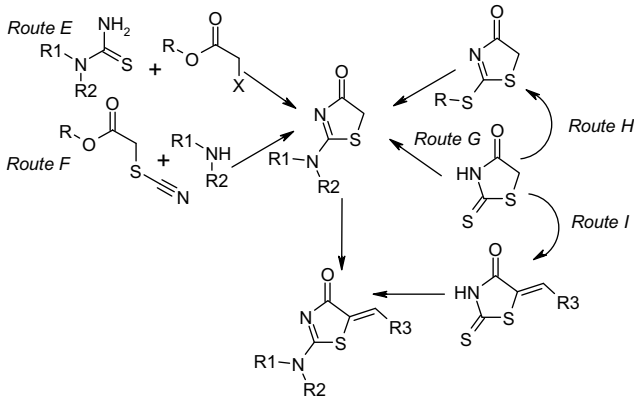
Figure 1. 2-Amino-5-alkylidene-thiazol-4-one.



Scheme 1. 2-Amino-5-alkylidene-thiazol-4-ones from acyclic precursors.

Keywords: Solid-phase synthesis; Traceless linker; Thiazolone; Knovenagel reaction.
* Corresponding author. Tel.: +39 0331 58 1216; fax: +39 0331 58 1757; e-mail: maurizio.pulici@nervianoms.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.02.059



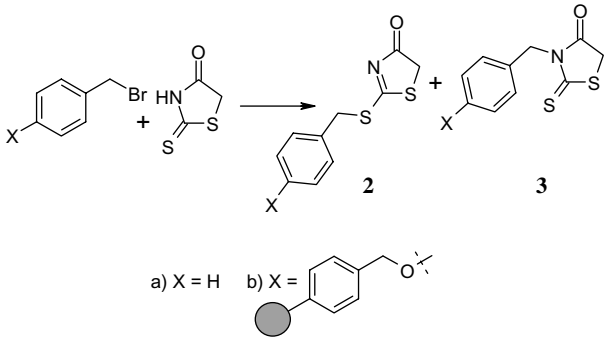
Scheme 2. 2-Amino-5-alkylidene-thiazol-4-ones by functionalization of thiazolones.

with an alkyl α-haloacetate and an aldehyde (*Route D*).[7a]

The latter synthesis can be performed also in a step-wise manner. Thus, the reaction between a thiourea and alkyl α-haloacetate yields an aminothiazolone (*Route E*)[11] that subsequently undergoes a Knovenagel reaction.[3,4d,7b,d–f] The aminothiazolone is also accessible through a reaction between alkyl thiocyanoacetate and an amine (*Route F*)[12] however, most commonly, it is synthesized starting from rhodanine, which is reacted directly with amines (*Route G*)[3,13] or after activation via alkyl thioether (*Route H*).[3a,7d–f] On the other hand, this sequence can be reversed by first condensing rhodanine with an aldehyde (*Route I*)[3,14] and then reacting it with an amine[3,13]

Despite such a great deal of synthetic routes and of applications in the field of medicinal chemistry, we are not aware of solid-phase protocols enabling the high-throughput synthesis of these compounds. Here we wish to disclose the development and implementation of a methodology allowing for the traceless synthesis of parallel arrays of two-diversity point aminothiazolones.

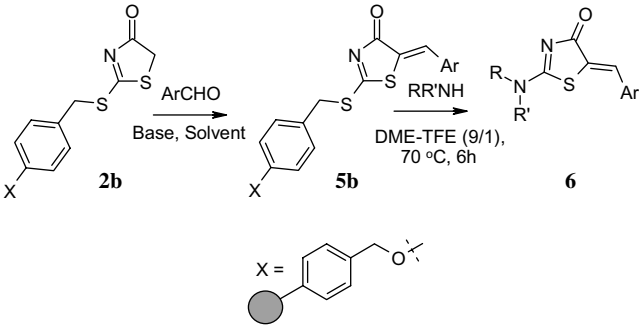
Thus rhodanine was reacted with bromo-Wang resin (4-(bromomethyl)phenoxymethyl polystyrene) to form the thioether **2b** (Scheme 3). The reaction in DMF under basic conditions proceeded with 83% yield with respect to the declared initial loading,[15] and a TFA-mediated cleavage (20% in DCM) of an analytical sample led to the removal of rhodanine only. However, an exhaustive piperidine-mediated cleavage led to the recovery of only 80% of the expected 2-piperidin-1-yl-thiazol-4-one,[16] which suggested the presence of some isomeric benzyl rhodanine **3b**. MAS-^{1}H NMR (CD_2Cl_2) spectrum of the resin showed indeed two diagnostic signals at 4.48 and 5.05 ppm (79–21 ratio) corresponding to benzylic methylenes. These were also in agreement with those observed for **2a** and **3a** attained in the 8–2 ratio[17] by performing a model reaction in solution between rhodanine and benzyl bromide.



Scheme 3. Loading of rhodanine on bromo-Wang resin: rhodanine 3.5 equiv, DIEA 5 equiv; DMF, rt, 18 h.

The subsequent steps of the synthetic routes comprised a Knovenagel condensation followed by an amine-mediated cleavage off the resin (Scheme 4); the latter clearly affects only compounds **5b**, while **3b** and its derivatives remain eventually anchored to the solid support.

The Knovenagel condensation required fine-tuning of the experimental conditions to avoid premature cleavage from the resin, a problem always met when using nucleophilic bases. Permutation of base, solvent, and temperature led to the following conclusions: alkoxides, even *t*-butoxide, does not work well regardless of the solvent used. The best bases are the organic ones (TEA; DIEA; DBU) in DCM at room temperature, or also phosphazene, in aprotic dipolar solvents. Time affects the outcome of the reaction, as short reaction times are associated with incomplete conversions, and, on the other hand, long reaction times give rise to compounds **7** as side products (Fig. 2).[18] The latter may arise from the nucleophilic displacement of an alkylidene thiazolone group from the resin by means of the anion generated on a second thiazolone moiety. Interestingly the amount of this type of side product depended also on



Scheme 4. Solid-phase synthesis of 2-amino-5-alkylidene-thiazol-4-ones.

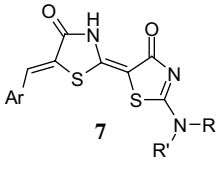


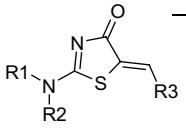
Figure 2. Structure of possible side products.

the temperature and on the strength of the bases: in both cases the higher the greater.

Eventually the optimized conditions for the Knovenagel condensation comprised the use of DCM as the solvent and DIEA as the base; the reaction was carried out using an excess of aldehyde (normally 5–8 equiv) for about 40 h. These conditions worked well for all aldehydes but were not effective for ketones. Only the thermodynamically more stable *Z*-isomers were obtained,[3a,7f,19] while the supposed *E*-isomers were occasionally observed in the HPLC trace (of final product **6**) but never isolated.

Liberation of products **6** from resin was achieved by reaction of **5** with an amine. With this strategy the otherwise stench thiols remain anchored to the solid support, providing an additional advantage to the present methodology. We typically used excess of reactant (3 equiv) in DME as a solvent with 10% trifluoroethanol (TFE) as a co-solvent at 70 °C.[20] Expected products could be isolated using chromatographic methods: either (mass-triggered) preparative HPLC or filtration through a silica gel plug worked well. Alternatively, in several instances products could be obtained with reasonable purities simply by decantation of the solid material (taken up with ethyl ether or acetone) obtained after evaporation of the reaction crude. Tables 1 and 2 show representative examples of this methodology.

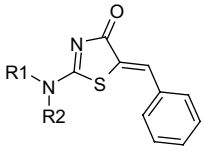
Table 1. Compounds **6**: examples with various aldehydes[a,b]



		R3 (from R3CHO)											
		a		b		c		d		e		f	
	R1R2N	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield
A		78	64[c]	100	81[c]	94	100[c]	77	70[c]	82	20[c]	91	26[c]
B		100	48[c]	95	89[c]	92	64[c]	95	41[c]	98	85[c]	80	34[d]
C		89	34[c]	92	40[c]			100	5[c]			100	43[d]

[a] Yield is determined on weight of isolated product and calculated on the effective loading of **2b**.
[b] Purity is evaluated by HPLC trace using UV detection at 220 nm.
[c] Purified by (mass triggered) preparative HPLC.
[d] Purified by filtration through a silica gel plug (DCM–MeOH 99:1).

Table 2. Compounds **6g**: examples with various amines[a,b]



	R1R2N											
	D		E		F		G		H		I	
	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield
	89	24[c]	100	24[c]	97	20[c]	96	20[c]	86	16[c]	100	22[e]
	J		K		L		M		N		O	
	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield	Purity	Yield
	76	12[d]	85	34[e]	93	27[c]	85	37[e]	100	10[d]	90	34[e]

[a] Yield is determined on weight of isolated product and calculated on the effective loading of **2b**.
[b] Purity is evaluated by HPLC trace using UV detection at 220 nm.
[c] Purified by (mass triggered) preparative HPLC.
[d] Purified by filtration through a silica gel plug (DCM–MeOH 99:1).
[e] Purified by decantation of the crude.

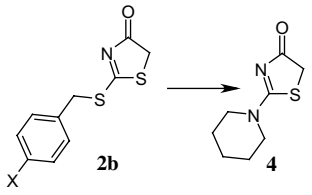
In conclusion we have developed a mild and practical protocol allowing for the high-throughput solid-phase synthesis of parallel arrays of 2-amino-5-alkylidene-thiazol-4-ones bearing two diversity points.

Acknowledgements

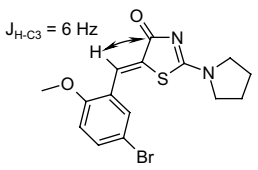
We thank Franco Ciprandi for the purification of products by preparative HPLC and Marco Tatò for recording MAS NMR spectra.

References and notes

1. According to a November 2004 SciFinder (http://www.cas.org/SCIFINDER/) search.
2. Ma, T.; Vetrivel, L.; Yang, H.; Pedemonte, N.; Zegarra-Moran, O.; Galietta, L. J. V.; Verkman, A. S. *J. Biol. Chem.* **2002**, *277*, 37235–37241.
3. (a) Hu, B.; Malamas, M.; Ellingboe, J.; Largis, E.; Han, S.; Mulvey, R.; Tillett, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 981–984; (b) Hu, B.; Malamas, M.; Ellingboe, J. *Heterocycles* **2002**, *57*, 857–870.
4. (a) Soltero-Higgin, M.; Carlson, E. E.; Phillips, J. H.; Kiessling, L. L. *J. Am. Chem. Soc.* **2004**, *126*, 10532–10533; (b) Hu, Y.; Helm, J. S.; Chen, L.; Ginsberg, C.; Gross, B.; Kraybill, B.; Tiyanont, K.; Fang, X.; Wu, T.; Walker, S. *Chem. Biol.* **2004**, *11*, 703–711; (c) Kocabalkanlia, A.; Ates, Ö.; Ötükb, G. *Arch. Pharm.* **2001**, *334*, 35–39; (d) Ates, Ö.; Altintas, H.; Ötükb, G. *Arzneim.-Forsch.* **2000**, *50*, 569–575.
5. Abdel-Ghani, E. *J. Chem. Res. Synop.* **1999**, *3*, 174–175.
6. (a) Andreani, A.; Rambaldi, M.; Leoni, A.; Locatelli, A.; Bossa, R.; Chiericozzi, M.; Galatulas, I.; Salvatore, G. *Eur. J. Med. Chem.* **1996**, *31*, 383–387; (b) Andreani, A.; Rambaldi, M.; Locatelli, A.; Leoni, A.; Bossa, R.; Chiericozzi, M.; Galatulas, I.; Salvatore, G. *Eur. J. Med. Chem.* **1993**, *28*, 825–829.
7. (a) Nasr, M. N. A.; Said, S. A. *Arch. Pharm.* **2003**, *336*, 551–559; (b) Martin, L.; Rabasseda, X.; Castaner, J. *Drugs Future* **1999**, *24*, 853–857; (c) Marchini, F. *Curr. Opin. Anti-Inflamm. Immunol. Invest. Drugs* **1999**, *1*, 64–68; (d) Song, Y.; Connor, D. T.; Doubleday, R.; Sorenson, R. J.; Sercel, A. D.; Unangst, P. C.; Roth, B. D.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem.* **1999**, *42*, 1151–1160; (e) Janusz, J. M.; Young, P. A.; Ridgeway, J. M.; Scherz, M. W.; Enzweiler, K.; Wu, L. I.; Gan, L.; Chen, J.; Kellstein, D. E.; Green, S. A.; Tulich, J. L.; Rosario-Jansen, T.; Magrisso, I. J.; Wehmeyer, K. R.; Kuhlenbeck, D. L.; Eichhold, T. H.; Dobson, R. L. M. *J. Med. Chem.* **1998**, *41*, 3515–3529; (f) Unangst, P. C.; Connor, D.; Cetenko, W. A.; Sorenson, R. J.; Kostlan, C. R.; Sircar, J. C.; Wright, C. D.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1994**, *37*, 322–328.
8. Khare, R. K.; Srivastava, M. K.; Singh, H. *Indian J. Chem., Sect. B* **1995**, *34*, 828–831.
9. (a) Hendrickson, J. B.; Rees, R.; Templeton, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 107–111; (b) Hurst, D. T.; Atcha, S.; Marshall, K. L. *Aust. J. Chem.* **1991**, *44*, 129–134; (c) Sarodnick, G.; Heydenreich, M.; Linker, T.; Kleinpeter, E. *Tetrahedron* **2003**, *59*, 6311–6321.
10. Dzurilla, M.; Kristian, P.; Imrich, J.; Stec, J. *Collect. Czech. Chem. Commun.* **1983**, *48*, 3134–3139.
11. (a) Seebacher, W.; Belaj, F.; Saf, R.; Brun, R.; Weis, R. *Monat. Chem.* **2003**, *134*, 1623–1628; (b) Iwataki, I. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3218–3220.
12. (a) Roessler, A.; Boldt, P. *Synthesis* **1998**, 980–982; (b) Zimmermann, T.; Fischer, G. W.; Olk, B. *J. Prakt. Chem.* **1990**, *332*, 540–546.
13. Taylor, E. C., Jr.; Wolinsky, J.; Lee, H.-H. *J. Am. Chem. Soc.* **1954**, *76*, 1870–1872.
14. (a) Vachal, P.; Pihera, P.; Svoboda, J. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1468–1480; (b) Tashima, T.; Kagechika, H.; Tsuji, M.; Fukasawa, H.; Kawachi, E.; Hashimoto, Y.; Shudo, K. *Chem. Pharm. Bull.* **1997**, *45*, 1805–1813; (c) Simpson, J.; Rathbone, D. L.; Billington, D. C. *Tetrahedron Lett.* **1999**, *40*, 7031–7033; (d) Murata, M.; Fujitani, B.; Mizuta, H. *Eur. J. Med. Chem.* **1999**, *34*, 1061–1070; (e) Gant, E. B.; Guiadeen, D.; Baum, E. Z.; Foleno, B. D.; Jin, H.; Montenegro, D. A.; Nelson, E. A.; Bush, K.; Hlasta, D. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2179–2182.
15. Reaction conditions were not optimized, however, in qualitative terms, DMF was more efficient than DCM, and DIEA gave a cleaner reaction than K_2CO_3 and NaOH. Typical loading procedure: To a suspension of bromo-Wang resin (1 g, declared loading 1.4 mmol/g) in DMF (15 mL), rhodanine (652 mg, 3.5 equiv) is added followed by DIEA (500 μL, 362 mg, 2 equiv). The mixture is gently shaken for 40 h. The resin is filtered, washed with DMF, MeOH, DCM, and dried in vacuo. Obtained



1.058 g (calculated loading 1.092 mmol/g, theoretical loading 1.303 mmol/g, 83%).
16. The resin obtained as reported in Ref. 15 (150 mg, 0.1638 mmol) was treated with excess piperidine (150 μL, 9.3 equiv) in DME–TFE (9:1) at 70 °C for 3 h. The product was then isolated by silica gel chromatography (DCM–MeOH 98:2): 24.7 mg (0.134 mmol, 82 %). No further product was recovered on reiteration.
17. Compounds **2a** and **3a** have been separated by silica gel chromatography (hexane–ethyl acetate 7:3). Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.99 (s, 2H) 4.58 (s, 2H) 7.25–7.32 (m, 5H); ^{13}C NMR (75 MHz $CDCl_3$) δ ppm 38.6, 40.0, 128.6, 129.4, 129.7, 135.3, 187.7, 201.8. Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.98 (s, 2H) 5.18 (s, 2H) 7.25–7.33 (m, 5H); ^{13}C NMR (75 MHz $CDCl_3$) δ ppm 35.8, 48.0, 128.4, 128.9, 129.5, 135.2, 174.0, 201.3. In addition only **2a** (and not **3a**) reacts completely with pyrrolidine (DME–TFE 9:1, 70 °C, 1 h) according to



the scheme of Ref. 16.
18. (a) Compounds with this general structure are known: Kandeel, K. A.; Youssef, A. M.; El-Bestawy, H. M.;

Omar, M. T. *J. Chem. Res. Synop.* **2003**, 682; (b) Kandeel, K. A.; Youssef, A. M.; El-Bestawy, H. M.; Omar, M. T. *Monat. Chem.* **2002**, *133*, 1211–1219.
19. Calculation of the H–C coupling constant is in good agreement with this stereochemistry:
20. The whole synthetic sequence has been carried out using either vials, Argonaut Quest 210, or Bohdan Miniblocks. Typical procedure for the 2-amino-5-alkylidene-thiazol-4-ones synthesis: 150 mg of the resin obtained as reported in Ref. 15 was suspended in DCM (3 mL) and the aldehyde (100 mg or μL) was added. Next DIEA (100 μL) was added and the mixture gently shaken for 40 h. The resin was washed successively with DMF, MeOH, and DCM (three times each). The resin was then slurried in DME–TFE (9:1) and treated with the amine (100 mg or μL) and heated at 70 °C for 6 h. The cleaved material was then isolated and the resin rinsed once with DCM–MeOH (9:1). Solvent was removed in vacuo yielding the reaction crude that was purified as mentioned in the text.