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2,4-Disubstituted-5-acetoxythiazoles: useful intermediates for the synthesis of thiazolones and 2,4,5-trisubstituted thiazoles

Q. Qiao, R. Dominique *, R. Goodnow Jr.

Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ 07110-1199, USA

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Abstract

A variety of 2,4-disubstituted-5-acetoxythiazoles were prepared from the substituted methyl benzoates in good to moderate yields using a three-step sequence: (1) ester to thionoester conversion, (2) coupling with an amino acid, and (3) acetic anhydride mediated cyclization. In situ hydrolysis and alkylation of 2,4-disubstituted-5-acetoxythiazoles afforded the corresponding thiazolones and 2,4,5-trisubstituted thiazoles. This methodology can be readily applied to the synthesis of thiazole-based chemical libraries.

Keywords: Thiazole; Thiazolone; Thionation method; Microwave irradiation; Chemical libraries

1. Introduction

The thiazole ring system is commonly found in many pharmaceutically important molecules. Numerous natural products containing this heterocycle have been isolated and exhibit significant biological activities such as cytotoxic, immunosuppressive, antifungal, and enzyme inhibitory activity.[1] Moreover, among the different aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process[2] and this ring structure is found in several marketed drugs. It can also be used in a scaffold hopping strategy[3] or as an amide isostere[4] during the course of probing structure activity relationships for lead optimization. As a result, thiazoles are frequently included in the design or are used as a core structure for the synthesis of chemical libraries.[5]

In the course of a lead generation effort, we required a flexible method, amenable to the high throughput chemical synthesis of appropriately substituted 2,4,5-trisubstituted thiazoles.

While a number of synthetic strategies have been developed for the synthesis of thiazoles, especially for 2,4-disubstituted thiazoles, which are generally assembled using the Hantzsh reaction,[6] fewer recent methods are available for the preparation of 2,4-disubstituted-5-acetoxy thiazoles.[7] Generally, these methods are impeded by the lack of commercially available thionobenzoate derivatives and the prolonged heating conditions required for the conversion of benzoate to thionobenzoate with traditional methods. To circumvent these problems, we investigated for alternative ways to prepare the desired thionobenzoate derivatives required to have access to 2,4-disubstituted-5-acetoxythiazoles With the development of microwave heating technology,[8] Polshettiwar et al.[9] reported a milder microwave assisted thionation method using phosphorous pentasulfide and hexamethyldisiloxane (HMDO). Further, Varma and Kumar[10] reported an expeditious, solvent-free method using Lawesson's reagent[11] under microwave irradiation.

Herein, we report a convenient three-step sequence (Scheme 1) to provide access to a diverse array of 2,4-disubstituted-5-acetoxythiazoles containing aryl, heteroaryl, and alkyl substitutions in moderate to good yields. Alternatively, in situ hydrolysis and alkylation of 2,4-disubstituted-5-acetoxythiazoles afforded the

* Corresponding author. Tel.: +1 973 235 3231.
E-mail address: romyr.dominique@roche.com (R. Dominique).

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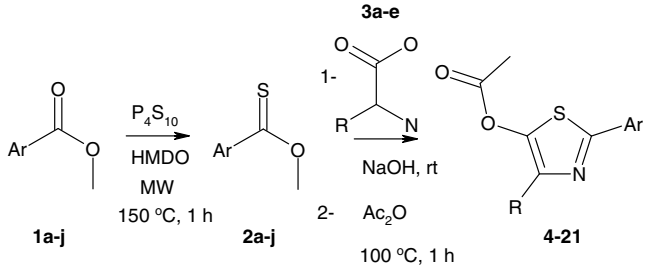


Scheme 1. Synthesis of 2,4-disubstituted-5-acetoxythiazoles.

corresponding thiazol-5-ones or 2,4,5-trisubstituted thiazoles as a major product depending on the type of electrophile used in the alkylation reaction.

2. Results and discussion

From the commercially available methyl benzoate derivatives and with racemic phenylglycine, a variety of 2,4-disubstituted-5-acetoxythiazoles were prepared in good to moderate yields using the following protocol (Table 1).

Table 1
Yields obtained for the preparation of thionoesters and 2,4-disubstituted-5-acetoxythiazoles using phenylglycine as amino acid

Entry		Yield (%)	Product		Yield (%)
1	**2a**[12b]	48	AcO	**4**[7b]	51
2	**2b**	28	AcO	**5**	80
3	**2c**[13a]	51	AcO	**6**	14 (27)[a]
4	**2d**[13b]	66	AcO	**7**	18
5	**2e**	55	AcO	**8**	64[a]
6	**2f**	46	AcO	**9**	16[a]
7	**2g**	51	AcO	**10**	42
8	**2h**[13c]	7	AcO	**11**	12
9	**2i**	13	AcO	**12**	4

[a] 4 equiv of **3a** was used.

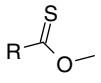
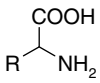
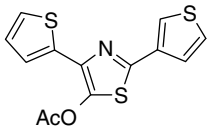
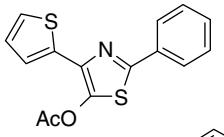
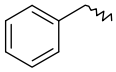
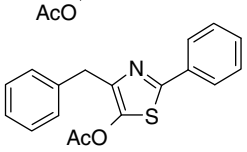
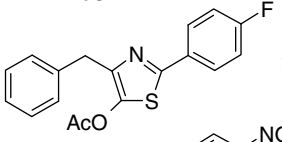
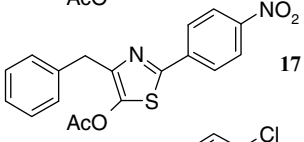
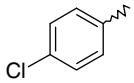
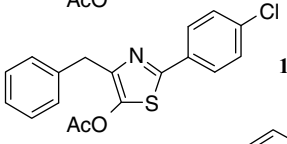
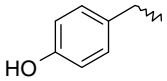
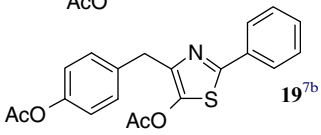
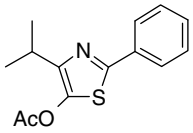
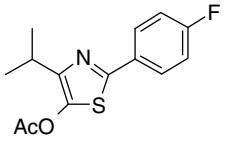
The first step consisted in converting a methyl benzoate into a thionoester. This type of conversion is generally the most difficult thionation reaction due to the low reactivity of the ester carbonyl group toward the usual thionation reagents such as Lawesson's reagent, contrary to the relatively short time for thionation of amides. As an alternative to Lawesson's reagent, we considered the P_4S_{10}/HMDO[12] combination under microwave irradiation at 150 °C, which provided the desired thionoester in approximately 1 h. The purified thionoester is then subjected to the next step with phenylglycine to afford the desired 2,4-disubstituted-5-acetoxythiazoles. The coupling is accomplished using a two-phase reaction mixture composed of 3 N NaOH and ether. Through acid–base liquid–liquid extraction, the coupled product was obtained and treated subsequently with acetic anhydride to give the desired thiazole derivatives.

As shown in Table 1, various substitutions could be obtained at position 2 on the thiazole ring by simply substituting the initial methyl benzoate derivatives. The unsubstituted phenyl group (entry 1) afforded a reasonable 51% yields of the thiazole. Various methyl benzoate derivates bearing electron-withdrawing groups at the *para* position were used to prepare the 2,4-disubstituted-5-acetoxythiazoles. The best yields were obtained with 4-fluoro-methyl benzoate (entry 2). In the case of the cyano derivative (entry 9), the very low yield is explained by the fact that the hydrolysis of the cyano group to the acid was observed. Using methyl benzoate derivatives having an electron-donating group at the *para* position such as methyl and methoxy groups (entries 3 and 4) gave modest yields of the 2,4-disubstituted-5-acetoxythiazoles. However, it was observed that by using 4 equiv of phenylglycine resulted in a slight increase in the yields. The same effect was observed for entries 5 and 6. Interestingly, the 3-bromomethyl benzoate gave a satisfying 64% yield of the desired thiazole bearing a bromo substituent, which could be used

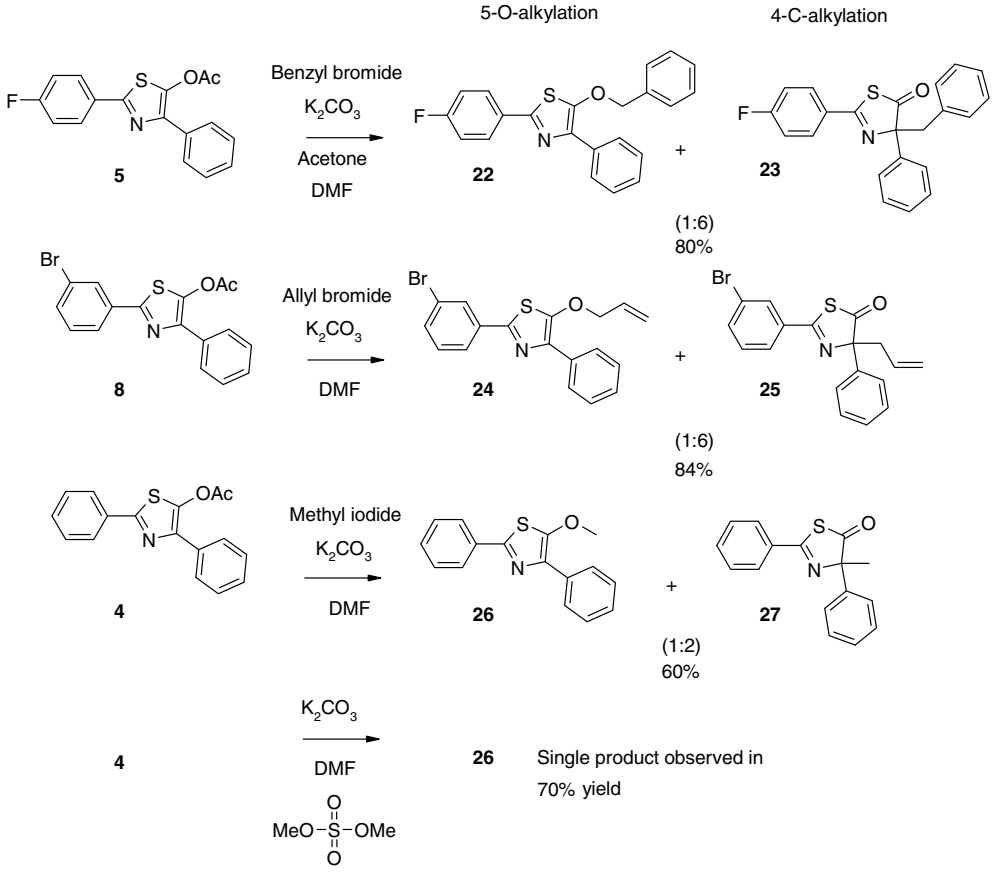
as a handle for further elaboration. Replacement of the phenyl group by a thiophene ring did not affect the yields for the formation of the desired thiazole (entry 7).

To expand the scope of this methodology, several other amino acids were investigated for the preparation of 2,4-disubstituted-5-acetoxythiazoles. The results are summarized in Table 2. D,L-α-aminothiophene-2-acetic acid gave modest yields of the corresponding thiazole composed of three heterocycles (entries 1 and 2). Phenylalanine (entries 3–6) was chosen as the coupling partner in order to introduce a benzylic substituent on the thiazole ring and to add one rotatable bond to make the scaffold less rigid. The best yields were obtained with the 4-fluoro-thionobenzoate, which was also true with entry 2 shown in Table 1, suggesting that the yields are not affected by changing a phenyl to a benzyl group. Tyrosine was also used and as expected, the free hydroxyl group was acetylated during the cyclization (entry 7). Encouraged by these results, we next investigated the use of an amino acid such as valine (entries 8 and 9) to prepare alkyl substituted thiazoles. Similar to our previous results, the cyclization occurred smoothly affording the desired thiazoles in modest yields.

Table 2
Yields obtained for the preparation of 2,4-disubstituted-5-acetoxythiazoles with various amino acids

Entry			Product	Yields
1	**2g**	 **3b**	 **13**	57
2	**2a**	**3b**	 **14**	30
3	**2a**	 **3c**	 **15**	41
4	**2b**	**3c**	 **16**	81
5	**2h**	**3c**	 **17**	23
6	 **2j**[13a]	**3c**	 **18**	55
7	**2a**	 **3d**	 **19**[7b]	33[a]
8	**2a**	 **3e**	 **20**	26
9	**2b**	**3e**	 **21**	56

[a] 4 equiv of **3d** was used.



Scheme 2. Synthesis of thiazol-5-ones and 2,4,5-trisubstituted thiazoles.

As shown in Tables 1 and 2, a wide range of 2,4-disubstituted-5-acetoxythiazoles can be synthesized using our methodology. However, we were concerned about the stability of the 5-acetoxy group to basic conditions and we envisioned that further derivatization would enlarge the utility of this methodology.

In situ hydrolysis of the acetoxy group in thiazole **5** using potassium carbonate as a base and an alkylating agent such as benzyl bromide in a mixture of DMF and acetone afforded an 80% yield of trisubstituted thiazole **22** and thiazol-5-one **23** in a 1:6 molar ratio not separable by column chromatography (Scheme 2). The ratio of the mixture was determined by the inspection of the ^1H NMR spectra in $CDCl_3$, which revealed clearly a characteristic singlet for the O–CH_2–Ph moiety at 5.22 ppm for the 2,4,5-trisubstituted thiazole **22**, whereas a doubled doublet was revealed for the C–CH_2–Ph moiety at 3.65 ppm for the 2,4,4-trisubstituted-thiazol-5-one **23**. The use of other alkylating agents such as methyl iodide and allyl bromide also gave a mixture of the corresponding thiazol-5-ones and 2,4,5-trisubstituted thiazoles. Similarly, the thiazol-5-one was found to be the major product in both cases.Therefore, under these conditions, the formation of the C-alkylation product is preferred over the O-alkylation product.

We were also interested in finding conditions that would favor the O-alkylation product. We envisioned that the formation of 2,4,5-trisubstituted thiazoles could be achieved by simply using hard electrophiles such as dimethyl sulfate. Indeed, when **4** was treated with dimethylsulfate and potassium carbonate in DMF, only the O-alkylation product was observed giving a 70% yield of the 2,4,5-trisubstituted thiazole.

3. Conclusion

In conclusion, we have developed a general and convenient three-step sequence, which gives access to a variety of 2,4-disubstituted-5-acetoxythiazoles containing aryl, heteroaryl, and alkyl substitution in moderate to good yields.[14] We have also shown that we can convert the 2,4-disubstituted-5-acetoxythiazoles into thiazol-5-ones and 2,4,5-trisubstituted thiazoles.[15,16] This methodology is highly flexible and amenable to the high throughput chemical synthesis of thiazole-based libraries. With the use of proper functional groups on methyl benzoate derivatives, amino acids, and alkylating agent, various points of diversification can be introduced to generate more complex molecules with interesting biological properties.

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14. *Representative procedure for the synthesis of 2,4-disubstituted-5-acetoxythiazoles*: A mixture of methyl 3-bromo-benzoate (2.0 g, 9.3 mmol), P_4S_{10} (1.03 g, 2.32 mmol), HMDO (3.2 mL, 14.9 mmol) was sealed in a tube. The sealed vial was heated by microwave irradiation (Emrys optimizer) for 60 min at 150 °C. The crude reaction mixture was then passed through a column of silica gel. Thionoester **2e** (1.1 g, 55%) was eluted using 0–20% ethyl acetate/hexanes.

   To thionoester **2e** (300 mg, 1.3 mmol) in 5 mL of ether were added 10 mL of 3 N NaOH and D,L-α-phenylglycine (784 mg, 5.19 mmol). The reaction mixture was stirred vigorously for 18 h at room temperature. The aqueous layer was separated, acidified with 10% HCl, and diluted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The oil obtained was then dissolved in acetic anhydride (5 mL) and heated at 100 °C for 1 h. The reaction mixture was evaporated to afford 310 mg (64%) of the desired thiazole **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H, CH_3), 7.32 (t, $J = 7.9$ Hz, 1H, aromatic), 7.38 (m, 1H, aromatic), 7.49 (m, 2H, aromatic), 7.55 (ddd, $J = 7.9$ Hz, $J = 1.8$ Hz, $J = 1.0$ Hz, 1H, aromatic), 7.87 (ddd, $J = 7.9$ Hz, $J = 1.8$ Hz, $J = 1.0$ Hz, 1H, aromatic), 8.04 (m, 2H, aromatic), 8.18 (t, $J = 1.8$ Hz, 1H, aromatic). HRMS (ES+) *m/z* calcd for $C_{17}H_{12}NO_2SBr$ $[M+H]^+$ 373.9845, obsd 373.9844.
15. *Representative procedure for the synthesis of thiazol-5-ones and 2,4,5-trisubstituted thiazoles*: To thiazole **4** (100 mg, 0.34 mmol), K_2CO_3 (234 mg, 1.69 mmol) in 2 mL of DMF was added dimethyl sulfate (64 μL, 0.68 mmol). The reaction mixture was stirred and heated at 50 °C for 1 h, then cooled down. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude material was then purified by column chromatography using 10% ethyl acetate/hexanes as eluent system to afford 65 mg (70%) of 2,4,5-trisubstituted thiazole **26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08 (s, 3H, CH_3), 7.31 (m, 1H, aromatic), 7.37–7.48 (m, 5H, aromatic), 7.93 (m, 2H, aromatic), 8.13 (m, 2H, aromatic); ^{13}C (100 MHz, $CDCl_3$): δ 63.9, 125.5, 126.8, 126.9, 128.2, 128.7, 129.2, 133.8, 134.1, 135.6, 153.0, 157.4. HRMS (ES+) *m/z* calcd for $C_{16}H_{13}NOS$ $[M+H]^+$ 268.0791, obsd 268.0790.
16. For **25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10 (m, 2H, CH_2), 5.11 (m, 1H, vinylic), 5.19 (m, 1H, vinylic), 5.71 (m, 1H, vinylic), 7.32–7.44 (m, 4H, aromatic), 7.55 (m, 2H, aromatic), 7.71 (ddd, $J = 8.0$ Hz, $J = 2.0$ Hz, $J = 1.1$ Hz, 1 H, aromatic), 7.82 (ddd, $J = 7.8$ Hz, $J = 1.7$ Hz, $J = 1.1$ Hz, 1 H, aromatic), 8.1 (dd, $J = 2.0$ Hz, $J = 1.7$ Hz, 1H, aromatic); ^{13}C (100 MHz, $CDCl_3$): 44.5, 91.3, 120.2, 123.1, 125.6, 127.1, 128.4, 128.6, 130.3, 130.6, 130.9, 135.0, 135.1, 137.4, 162.2, 207.9. HRMS (ES+) *m/z* calcd for $C_{18}H_{14}NOSBr$ $[M+H]^+$ 372.0052, obsd 372.0052.