An Improved Procedure for the Preparation of Alkyl *N*-(4-Aryl-2-thiazolyl)oxamates

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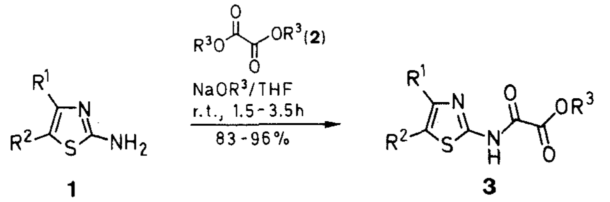
2-Amino-4-arylthiazoles react cleanly with dialkyl oxalates in the presence of sodium alkoxides at room temperature to afford alkyl *N*-(4-aryl-2-thiazolyl)oxamates in high yield.

A number of oxamic acid derivatives have been reported as orally-active antiallergy agents,[1-6] including the thiazolyloxamate Tioxamast (INN) (**3c**) which is currently undergoing clinical investigation. We therefore required kilogram quantities of **3c** using procedures compatible with subsequent large-scale production.

Thiazolyloxamates of structure **3** have been prepared from 2-aminothiazoles by reaction with alkyl oxalyl chlorides.[4,5] The method, however, gives variable yields of oxamates and on a large scale suffers the disadvantage of using an expensive and corrosive alkyl oxalyl chloride. The thermal condensation of an aminothiazole with a dialkyl oxalate has also been reported, but, in contrast to the facile reaction observed with alkylamines,[7,8] forcing conditions (20 h at 125 °C) are required and a large excess of oxalate is necessary to prevent dioxamide formation.[9] Similar results have been reported for the reaction of diethyl oxalate with a variety of aromatic amines, including 2-aminopyridine.[10]

We now report a simple, general method for the preparation of alkyl *N*-(4-aryl-2-thiazolyl)oxamates **3** by the reaction of 2 equivalents of dialkyl oxalates **2** with 2-aminothiazoles **1** at room temperature in the presence of a sodium alkoxide.



3	R^1	R^2	R^3	3	R^1	R^2	R^3
a	2-pyridyl	H	Et	**g**	4-HOC_6H_4	H	Et
b	4-$MeOC_6H_4$	H	*t*-Bu	**h**	4-MeC_6H_4	H	Et
c	4-$MeOC_6H_4$	H	Et	**i**	3,4-$(MeO)_2C_6H_3$	H	Et
d	Ph	H	Et	**j**	3,4-$(OCH_2CH_2O)C_6H_3$	H	Et
e	Ph	Me	Et	**k**	4-$MeOC_6H_4$	H	Me
f	4-FC_6H_4	H	Et	**l**	4-$MeOC_6H_4$	H	Bu

The alkoxy group of the alkoxide should correspond to the alkoxy group of **3** in order to avoid transesterification. No reaction is observed at room temperature in the absence of the alkoxide, and at least one equivalent is necessary for optimal yields. The reaction is complete

Table. Alkyl *N*-(4-Aryl-2-thiazolyl)oxamates **3** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^1H-NMR (acetone-d_6/TMS) δ, J (Hz)
3a	1.5	92	141–142 (acetone/H_2O)	141–144[4]	1730, 1685	1.50 (t, 3H, J = 7), 4.52 (q, 2H, J = 7), 7.43 (m, 1H), 7.96 (m, 1H), 8.09 (s, 1H), 8.13 (m, 1H), 8.71 (m, 1H), 11.86 (s, 1H)
3b	3.5	83	167–168 (acetone/H_2O)	$C_{16}H_{18}N_2O_4S$ (334.4)	1740, 1690	1.72 (s, 9H), 3.95 (s, 3H), 7.10 (m, 2H), 7.57 (s, 1H), 7.98 (m, 2H), 11.58 (s, 1H)
3c	1.5	96	168–169 (acetone/*i*-Pr_2O)	164–165[4]	1735, 1695	1.50 (t, 3H, J = 7), 3.95 (s, 3H), 4.52 (q, 2H, J = 7), 7.11 (m, 2H), 7.59 (s, 1H), 8.00 (m, 2H), 11.72 (s, 1H)
3d	1.5	91	158–159 (acetone/H_2O)	158.5–160[4]	1745, 1680	1.50 (t, 3H, J = 7), 4.53 (q, 2H, J = 7), 7.55 (m, 3H), 7.76 (s, 1H), 8.06 (m, 2H), 11.78 (s, 1H)
3e	1.5	93	148–149 (acetone/H_2O)	$C_{14}H_{14}N_2O_3S$ (290.3)	1730, 1690	1.49 (t, 3H, J = 7), 2.68 (s, 3H), 4.51 (q, 2H, J = 7), 7.53 (m, 3H), 7.79 (m, 2H), 11.55 (s, 1H)
3f	1.5	94	222–223 (acetone/H_2O)	220–223[4]	1740, 1685	1.51 (t, 3H, J = 7), 4.53 (q, 2H, J = 7), 7.32 (m, 2H), 7.74 (s, 1H), 8.10 (m, 2H), 11.78 (s, 1H)
3g	1.5	92	232–233 (acetone/H_2O)	230–233[4]	1730, 1675	1.50 (t, 3H, J = 7), 4.52 (q, 2H, J = 7), 7.02 (m, 2H), 7.52 (s, 1H), 7.91 (m, 2H), 8.63 (s, 1H), 11.68 (s, 1H)
3h	1.5	93	170–171 (acetone/H_2O)	171[5]	1745, 1700	1.50 (t, 3H, J = 7), 2.46 (s, 3H), 4.52 (q, 2H, J = 7), 7.35 (m, 2H), 7.67 (s, 1H), 7.94 (m, 2H), 11.74 (s, 1H)
3i	1.5	89	131–132 (acetone)	131–133[4]	1730, 1695	1.50 (t, 3H, J = 7), 3.96 (s, 3H), 4.00 (s, 3H), 4.53 (q, 2H, J = 7), 7.11 (m, 1H), 7.63 (s, 1H), 7.77 (m, 2H), 11.75 (s, 1H)
3j	1.5	91	205–206 (acetone)	204–207[4]	1720, 1690	1.50 (t, 3H, J = 7), 4.41 (s, 4H), 4.52 (q, 2H, J = 7), 6.96 (m, 1H), 7.59 (m, 2H), 7.76 (s, 1H), 11.73 (s, 1H)
3k	3.0	93	178–179 (acetone/H_2O)	179[5]	1740, 1690	3.95 (s, 3H), 4.07 (s, 3H), 7.09 (m, 2H), 7.58 (s, 1H), 7.98 (m, 2H), 11.73 (s, 1H)
3l	1.5	96	145–146 (acetone/H_2O)	$C_{16}H_{18}N_2O_4S$ (334.4)	1735, 1690	1.08 (t, 3H, J = 7), 1.59 (m, 2H), 1.88 (m, 2H), 3.95 (s, 3H), 4.48 (q, 2H, J = 7), 7.09 (m, 2H), 7.58 (s, 1H), 7.99 (m, 2H), 11.73 (s, 1H)

[a] Yield of pure isolated product.

[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.16, N ±0.17.

within 4 hours at room temperature, compounds **3** being obtained in 83–96% yield, as shown in the Table. It is noteworthy that the method is applicable to *tert*-butyl esters and is compatible with pyridyl and phenolic substituents.

In conclusion, the method is rapid, the reaction conditions are mild, and the yields excellent.

All reagents and solvents were of reagent grade and were used without further purification. The 2-amino-4-arylthiazoles were prepared by the reaction of thiourea (Aldrich Chemical Co.) with the appropriate bromoketone.[5] Dialkyl oxalates were purchased from Aldrich Chemical Co. Melting points were determined using a Kofler block (Heizbank WME) and are uncorrected. IR spectra were recorded on a Philips Unicam SP3-2005 spectrophotometer and NMR spectra recorded using a Bruker AC-200 spectrometer. Microanalyses were obtained with a Carlo Erba Elemental Analyser 1106.

Ethyl *N*-[4-(4-Methoxyphenyl)-2-thiazolyl]oxamate (3c); Typical Procedure:

A 2N solution of NaOEt in EtOH (165 mL, 0.33 mol) is added with vigorous stirring to a mixture of diethyl oxalate (66.3 mL, 0.48 mol) and 2-amino-4-(4-methoxyphenyl)thiazole (50 g, 0.24 mol) in THF (500 mL) with external cooling (caution: EXOTHERM). The mixture is allowed to warm to r.t. and stirred for 1.5 h. The solvent is evaporated under reduced pressure and 2N AcOH (325 mL) added to the residue. The yellow solid obtained is collected by filtration and washed with H_2O (3 x 500 mL). The crude product is taken up in acetone (500 mL) and i-Pr_2O (500 mL) is added to the solution to precipitate **3c** which is collected by filtration, washed with i-Pr_2O (200 mL) and dried at 50°C under reduced pressure; yield: 71.22 g (96%); mp 168–169°C (Table).

The authors wish to thank Dr. J.P. Ribet and colleagues for analytical and spectroscopic data.

Received: 19 February 1991; revised: 8 May 1991

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