Simple One-Pot Synthesis of 2-Acylmethylidene-3-methylthiazolines[1]

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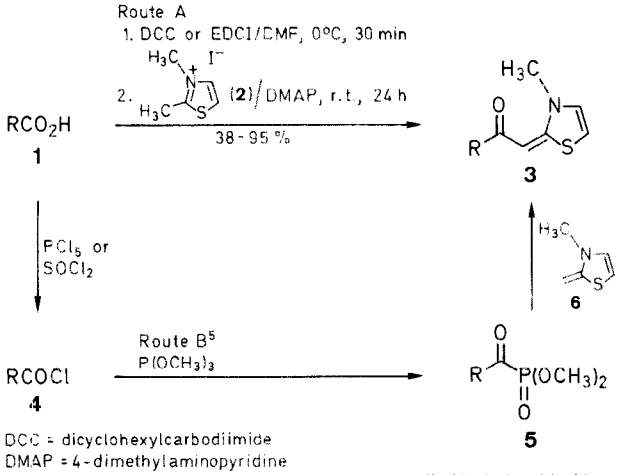
2-Acylmethylidene-3-methylthiazolines **3** (R = alkyl or aryl) are obtained from their precursor acids in one operation. Carboxylic acids **1** are activated with carbodiimide, and treated, *in situ*, in the presence of 4-dimethylaminopyridine, with 3-methyl-2-methylidene-4-thiazoline **(6)** (derived from thiazolium salt **2**) to yield 2-acylmethylidene-3-methylthiazolines **3**.

Compounds of novel structure, especially non-steroidals are being sought to augment existing therapies for rheumatoid arthritis and other inflammatory diseases.[3] Aromatic 2-acylmethylidene-3-methylthiazolines of general structure **3** are known to possess anti-inflammatory and analgesic properties.[4] As part of our program in this area we required easy access to 2-acylmethylidene-3-methylthiazolines of diverse structure including alkyl, arylalkyl, and substituted aryl derivatives.



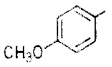
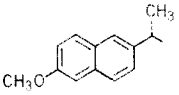
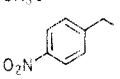
DCC = dicyclohexylcarbodiimide
DMAP = 4-dimethylaminopyridine
EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

Direct preparation of 2-acylmethylidenethiazolines from acid chlorides **4** is a low yield reaction, and the method of choice has been the conversion of phosphonates **5**[5] to the desired products. Since acid chlorides are generally less available than their precursor acids **1**, a three-step sequence is frequently required for the preparation of 2-acylmethylidene-3-methylthiazolines **3** from commercial starting materials (Route B of the reaction scheme[5]). In this paper we describe a novel one-pot procedure, which short circuits these extra steps. 2-Acylmethylidene-3-methylthiazolines **3**, both aryl and alkyl, were obtained from the precursor acids **1** in one operation; Route A of the reaction scheme.

Mild acylating agents of diverse structure (*O*-acylisoureas, mixed anhydrides, imidazolides, etc.) can be easily prepared from carboxylic acids *in situ*, are widely used in peptide synthesis,[6] and could be exploited for the conversion outlined in Route A. In fact carbodiimide activated acids reacted readily with 3-methyl-2-methylidene-4-thiazoline **(6)**, generated *in situ*, in the presence of 4-dimethylaminopyridine (DMAP) to yield the desired products. None of the presumed intermediates need be isolated and the reaction takes place in one vessel.

The reaction is carried out as follows. The organic acid is first reacted with the carbodiimide for thirty minutes, i.e. the optimal time for conversion of the acid to the acylating intermediate(s),[7]

Table 1. One-Pot Synthesis of 2-Acylmethylidene-3-methylthiazolines **3**

Product	R	Yield[a] (%)	mp (°C)[b] (EtOAc)	Molecular Formula[c] or Lit. mp (°C)
3a		62 (15)[e]	150.5–151.5[d]	149[5]
3b		57	140.5–141.5	141[4]
3c		60	126.5–128.5	$C_{13}H_{10}N_2OS$ (242.3)
3d		43	119–120	$C_{13}H_{13}NO_2S$ (247.3)
3e		58	99–103[d]	98[5]
3f		38	112–114	$C_{14}H_{13}NOS$[f] (243.3)
3g		57 (95)[g]	168–170	$C_{19}H_{19}NO_2S$ (325.4)
3h		no reaction	–	–
3i		62	86–87	$C_{10}H_{15}NOS$ (197.3)
3j		38	102–103	$C_{11}H_{13}NOS$ (207.3)
3k		78	oil[d]	oil[5]

[a] Isolated yield after column chromatography.
[b] Uncorrected, measured with a Büchi 510 melting point apparatus.
[c] Satisfactory microanalyses obtained: C ±0.29, H ±0.36, N ±0.25.
[d] ^{1}H-NMR spectra matches literature data.
[e] Triethylamine replaced by DMAP.
[f] Exact Mass: calc. 243.0718, found 243.0717; recorded on a MAT 8230 spectrometer.
[g] DCC replaced by EDCI.

the relative amount of *O*-acylisourea vs. anhydride formed has not been determined. DMAP and thiazolium salt **2**[8] are added, and the resulting pink to dark red colored reaction mixture is indicative of the formation of 3-methyl-2-methylidene-4-thiazoline (**6**). The latter attacks the activated carbonyl via the formal enamine carbon. Deprotonation of the resulting thiazolium salt to yield 2-acylmethylidene-3-methylthiazoline **3** is ensured by the presence of one equivalent of base. The preparation of 2-benzoylmethylidene-3-methyl-4-thiazoline (**3a**) illustrates the method.

A priori, any one of three species (*O*-acylisourea, anhydride, or acyl pyridinium salt) could serve as the acylating intermediate in this condensation. A catalytic role for DMAP is likely since acyl pyridinium salts are often invoked as intermediates in oxygen acylation reactions.[9] In fact when DMAP was replaced by triethylamine (Table 1), the yield of 2-benzoylmethylidene-3-methyl-4-thiazoline (**3a**) was poor; no product was detected when a 1,8-diazabicyclo[5.4.0]undec-7-ene/*N*-hydroxysuccinimide combination was used. The procedure is not restricted to simple aromatic acids, but is general (Table 1). Several heretofore unknown 2-acylmethylidene-3-methyl-thiazolines (Table 2) were prepared via Route A. Alkenyl, alkyl, benzylic and substituted aryl acids were all successfully converted to their respective products by this method. The only failure, entry **3h**, can be attributed to rapid deprotonation at the benzylic position upon addition of DMAP. Overall, the yields (after chromatography) are modest but compare favorably with the reported method.[5] For example **3a** and **3k** are obtained in 62% and 78% yields, respectively, by our method; 47% and 51% in two steps from the acid chloride.[5] To avoid the complications associated with the decreased stability[10] of water soluble carbodiimides, dicyclohexylcarbodiimide (DCC) was used as the activating agent in one experiment (Table 1, entry **3g**). The yield was much increased with this reagent. However, because repeated chromatography was required to remove the dicyclohexylurea by-product, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was identified as the reagent of choice.

Although carbodiimide mediated acylation reactions have been carried out with a variety of oxygen-[9,11,12] and nitrogen-centered nucleophiles,[6,11] the reaction presented here represents one of the few examples[8] of carbon–carbon bond formation via a presumed *O*-acylisourea intermediate. The utilization of DCC/DMAP for *C*-acylations in general has not, as yet, been systematically explored.

Table 2. Spectral Data of new 2-Acylmethylidene-3-methylthiazolines **3** Prepared

Compound	IR (KBr)[a] ν_{max} (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)
3c	2225, 1600, 1555, 1495, 1460, 1255	3.67 (s, 3H, CH_3N); 6.35 (d, 1H, J = 1.1, =CH); 6.59 (dd, 1H, J = 4.3, NCH =CHS); 6.94 (d, 1H, NCH=CHS); 7.4–7.8, 8.1–8.3 (2m, 4H_{arom})
3d	1605, 1545, 1480, 1250, 1165, 970, 835, 690	3.57 (s, 3H, CH_3N); 3.84 (s, 3H, OCH_3); 6.34 (d, 1H, J = 1.1, =CH); 6.44 (dd, 1H, J = 4.3, NCH=CHS); 6.82 (d, 1H, J = 4.3, NCH=SCH); 6.92, 7.96 (2m, 4H_{arom})
3f	1630, 1545, 1485, 1425, 1250, 1150, 995, 695	3.55 (s, 3H, CH_3N); 5.89 (d, 1H, J = 0.97, =CH); 6.50 (dd, 1H, J = 4.3, NCH=CHS); 6.84 (d, 1H, J = 4.3, NCH =CHS); 6.84 (d, 1H, J = 15.8, PhCH =CH); 7.2–7.6 (m, 5H, PhCH=CH); 7.63 (d, 1H, J = 15.8, PhCH=CH)
3g	1630, 1590, 1485, 1425, 1225, 1150, 1025, 970, 855, 700	1.61 (d, 3H, J = 7.1, CH_3CH); 3.31 (s, 3H, CH_3N); 3.89 (s, 3H, CH_3O); 3.94 (q, 1H, J = 7.1, CH_3CH); 5.62 (d, 1H, J = 1.0, =CH); 6.33 (dd, 1H, J = 4.3, NCH=CHS); 6.66 (d, 1H, J = 4.3, NCH =CHS); 7.0–7.8 (m, 6H_{arom})
3i	1575, 1475, 1415, 1250, 1160, 990, 710	0.90–1.0 [m, 6H, $CH(CH_3)_2$]; 1.9–2.4 [m, 3H, $CH(CH_3)_2$, CH_2CO]; 3.47 (s, 3H, CH_3N); 5.68 (d, 1H, J = 1.1, =CH); 6.36 (dd, 1H, J = 4.3, NCH=CHS); 6.75 (d, 1H, J = 4.3, NCH =CHS)
3j	1580, 1480, 1425, 1250, 1185, 1130, 695	2.55–2.75 (m, 4H, CH_2CHCH_2); 3.05–3.45 (m, 1H, CH_2CHCH_2); 3.47 (s, 3H, CH_3N); 5.68 (s, 2H, CH=CH); 5.72 (d, 1H, J = 1.2, =CH); 6.37 (d, 1H, J = 4.3, NCH=CHS); 6.76 (d, 1H, J = 4.3, NCH =CHS)

[a] Recorded on a Perkin-Elmer 298 IR spectrophotometer.
[b] Recorded on a Bruker WP-80 spectrometer.
[c] $[\alpha]_D^{23}$ + 157.2° ($CHCl_3$, c = 1.0); measured on a Rudolph Autopol III instrument.

2-Benzoylmethylidene-3-methyl-4-thiazoline (3a); Typical Procedure:
Benzoic acid (0.10 g, 0.82 mmol) is dissolved in dry DMF (10 mL) blanketed with argon, cooled in an ice bath and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.172 g, 0.90 mmol). The resulting suspension is warmed to room temperature, stirred for 30 min, then treated with DMAP (0.10 g, 0.82 mmol) and 2,6-dimethylthiazolium iodide (**2**;[8] 0.207 g, 0.86 mmol). The mixture is stirred overnight at room temperature to give a red solution, which is diluted with EtOAc (100 mL) and washed with brine (5 × 20 mL). The organic layer is dried (Na_2SO_4), concentrated, and the residue subjected to flash chromatography (50% EtOAc/*n*-hexane → EtOAc). Fractions containing the product (TLC, 75% EtOAc/*n*-hexane) are combined to afford 2-benzoylmethylidene-3-methyl-4-thiazoline (**3a**) as a yellow solid; yield: 0.11 g (62%). A recrystallized sample (EtOAc) showed mp, IR and ^{1}H-NMR identical to material prepared by the literature method.[5]

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