A multicomponent access to 1,3-thiazine-6-phenylimino-5-carboxylates

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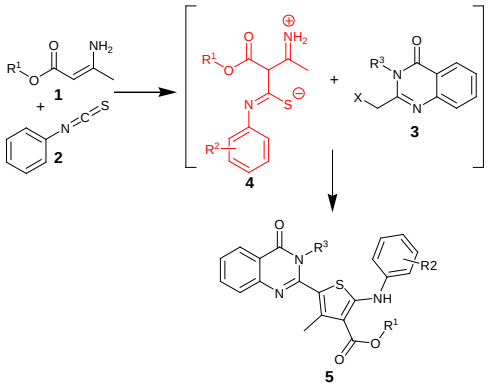
ABSTRACT

The multicomponent reaction of ethyl 3-aminocrotonate (**1**), substituted phenylisothiocyanates (**2a-i**) and acetic anhydride (**7**), afforded facile access to a series of substituted 1,3-thiazine-6-phenylimino-5-carboxylates under mild conditions in 15-65% yields. Limited tolerance for modification of the anhydride moiety was noted with significant reduction in yield for propionic and trifluoroacetic anhydrides. The use of benzoic anhydride favoured a two component coupling product.

Introduction

Isothiocyanate multicomponent reactions (MCRs) have proved to be extremely versatile entry points to a wide array of novel biologically active scaffolds.[1-4] MCRs, by virtue of this simplicity and the diversity of potential individual components can permit the exquisite positioning of key pharmacophoric moieties in the correct chemical space to enable critical interactions within protein binding site.[5-10]



Scheme 1. Reagents and conditions: THF:CH_3CN (1:1), 45-50 ºC, DMF

The use of a one-pot MCR is particularly appealing, especially in light of the increasing drivers towards sustainable synthetic methodologies and approaches with high atom economy.[11-14] We were particularly interested in a recent report from Vasu and co-workers that detailed the one-pot MCR synthesis of quinazolin-2-yl-tetrasubstituted thiophenes.[15] While the thiophene moiety has had widespread use in medicinal chemistry, it was the transient formation of the ammonium thiolate zwitterion (**4**) in the postulated mechanism that attracted our initial attention (Scheme 1).[16-18]

Examination of Vasu's proposed mechanism, suggested that replacement of the activated halide by acetic anhydride would permit *in situ* trapping of the anion, which would then follow a similar sequence of intramolecular additions to yield compounds such as **6**, or possibly those lacking the exocyclic -NH_2 (from loss of NH_3).[15] Thus our interest lay in the possible generation of a family of phenylimino-1,3-oxathiane-5-carboxylates (Figure 1), a scaffold that is currently very poorly described in the chemical literature.[19]

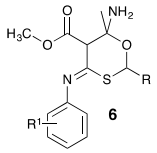
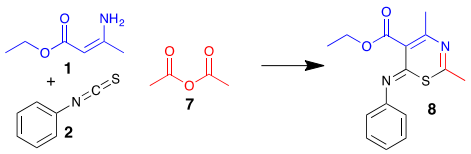


Figure 1. Representative example of a phenylimino-1,3-oxathiane-5-carboxylate.

Ethyl 3-aminocrotonate (**1**) was stirred with phenylisothiocyanate (**2**) under a nitrogen atmosphere followed by the addition of acetic anhydride (**7**). TLC analysis showed clear evidence for the consumption of starting materials, however, examination of the crude NMR showed no evidence of a NH_2 moiety, nor did the FTIR spectrum. No NH stretch was observed, but there was clear evidence of the ester C=O ($\upsilon_{C=O}$ 1728 cm^{-1}) and additional signals in the aromatic region of the spectrum. Rather than the proposed phenylimino-1,3-oxathiane-5-carboxylate, all spectroscopic evidence was consistent with the synthesis of a similarly poorly described scaffold, 2,4-dimethyl-6-phenylimino-6*H*-[1,3]thiazine-5-carboxylic acid ethyl ester (**8a**) which was isolated in a 65% yield (Scheme 2).[20]



Scheme 2. Synthesis of 1,3-thiazine (**8a**): Reagents and conditions: CH_3CN, 24 h, RT under N_2.

Most probably the observed 1,3-thiazine-6-phenylimino-5-carboxylate (**8a**) arose *via* the coupling of ethyl 3-aminocrotonate with phenyl isothiocyanate to yield the ammonium thiolate zwitterion (**10**). The thiolate was intercepted by the addition of acetic anhydride and following acetate loss and H-abstraction, yielded enamine (**12**). Under the reaction condition, either directly *via* protonation of the ketone, nucleophilic attach by the amine

moiety followed by protonation (2x) and subsequent loss of water affords the protonated 1,3-thiazine-6-phenylimino-5-carboxylate which is neutralized *via* acetate H-abstraction to give **8a**. This mechanism differs from Vasu's only in the final stages where the loss of ammonia is not favoured over intramolecular condensation with the carbonyl moiety (Figure 2).

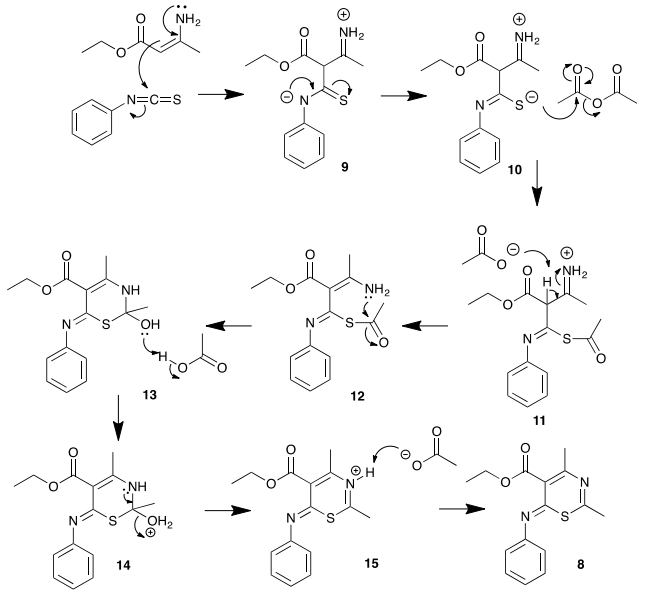
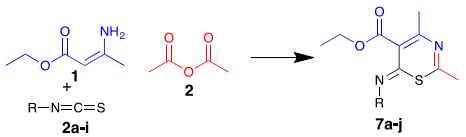
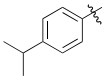
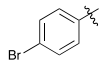
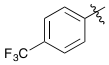
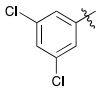
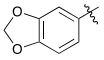


Figure 2. Proposed mechanism for the formation of 1,3-thiazine-5-carboxylate from the one pot MCR of ethyl 3-aminocrotonates, phenylisothiocyanate and acetic anhydride.

The use of a variety of substituted isothiocyanates afforded 1,3-thiazines **8a-8i** in low (15%, **8i**; Table 1, Entry 9;) to good (65%, **8a**; Entry 1) yields. The introduction of a bromine substituent (64%, **8d**; Entry 4) was well tolerated with no change in yield (65 vs 64%), but strong electron withdrawing substituents, e.g. 4-CF_3 (35%, **8e**; Table 1, Entry 5) and 3,5-Cl_2 (20%, **8f**; Entry 6) resulted in a significant reduction in yield. Both 3,4-methylenedioxy and 2-naphthyl isothiocyanates were reasonably tolerated with yields of 29% and 29%, respectively (**8g** and **8h**; Entries 7 and 8). Alkyl isothiocyanates were not well tolerated with the 1,3-thiazene-5-carboxylate originating from ethyl isothiocyanate obtained in low yield (15%, **8i**; Entry 9). The addition of additional equivalents of EtNCS, failed to increase the yield. The poor results in this instance meant that we did not further explore the use of alkyl isothiocyanates.

Table 1. Synthesis of substituted 1,3-thiazin-6-imino-5-carboxylates **8a-8i**.



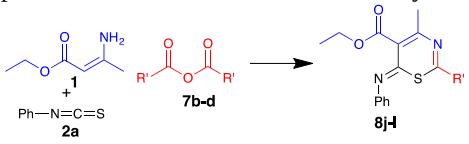
Entry	R	Product	Yield (%)
1		**8a**	65
2		**8b**	19
3		**8c**	50
4		**8d**	64
5		**8e**	35
6		**8f**	20
7		**8g**	29
8		**8h**	29
9		**8i**	15

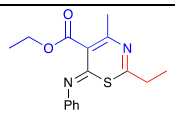
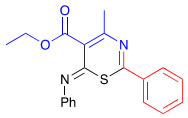
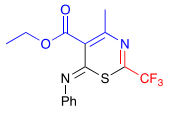
Reagents and conditions: CH_3CN, 24 h, RT under N_2

This path to 1,3-thiazine-6-phenylimino-5-carboxylates, unlike that reported by Vugts and co-workers,[21] and Glasnov and co-workers[22] does not require the use of harsh reagents (n-BuLi) nor low temperatures (-78 ºC; to generate the phosphonate anion) and thus represents a significantly more facile entry point.

To further explore the scope of this reaction we next examined modifications of the anhydride moiety. We examined the use of propionic, benzoic and trifluoroacetic anhydride and while 1,3-thiazine-6-imino-5-carboxylates **8j-8l** were isolated, they were typically in very low yields (4–29%; Table 2). This most likely is a consequence of the multiple roles that the anhydride moiety plays during the course of this reaction, including as an electrophile, with the corresponding carboxylate then acting as a base.

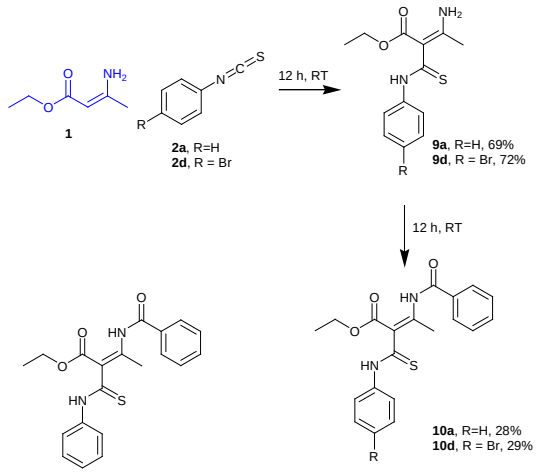
Table 2. Synthesis of substituted 1,3-thiazin-6-imines **8k-8l** using propionic, benzoic and trifluoroacetic anhydrides.



Entry	R'	Product	Yield (%)
1	CH_3CH_2 **7b**	 **8j**	29
2	 **7c**	 **8k**	4
3	CF_3 **7d**	 **8l**	12

Reagents and conditions: CH_3CN, 24 h, RT under N_2

In the case of benzoic anhydride, we further explored this reaction with phenyl- and 4-bromophenyl-isothiocyanate. In both instances the addition of the initial isothiocyanate (**2a** and **2d**) to ethyl 3-aminocrotonate (**1**) proceeded well with the thioamides formed in good yield (~70%). However, only limited evidence of thiolate interception was noted with the major isolated product arising from benzoylation of the free amino moiety (28%) (Scheme 3).



Scheme 3. Reagents and conditions: CH_3CN, 24 h, RT, under N_2

Conclusions

The reaction of ethyl 3-aminocrotonate (**1**), a range of phenyl isothiocyanates (**2a**-**m**) and acetic anhydride has provided a rapid access to 1,3-thiazine-6-phenylimino-5-carboxylates that avoids the use of strong bases and restrictive reaction conditions.[20] This synthesis, while tolerant of the phenyl isothiocyanate substituent has limited tolerance for modifications to the anhydride moiety. In the case of benzoic anhydride, preference for the generation of the *N*-benzoyl analogues was observed. Notwithstanding, the multicomponent synthesis of 1,3-thiazine-6-phenylimino-5-carboxyates was accomplished in low to good yields in a simple process requiring only stirring at room temperature.

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General procedure of synthesis, represented by **8a**: *2,4-Dimethyl-6-phenylimino-6H-[1,3]thiazine-5-carboxylic acid ethyl ester.* A mixture of ethyl 3-aminocrotonate (0.3 mL, 2.373 mmol) and phenyisothiocyanate (**2a**) (0.283 mL, 2.373 mmol) was stirred, under solvent free conditions, at room temperature overnight under a nitrogen atmosphere. To the stirred mixture was added acetic anhydride (0.26 mL, 2.61 mmol) and acetonitrile (5 mL). The reaction mixture was stirred for 24h at room temperature and the crude material was subjected to silica gel chromatography (1:4 ethyl acetate : petroleum ether) to afford **8a** (0.41 g, 65%) as a bright yellow solid (mp 145.3-146.5 ºC). IR (cm^{-1}): 2984 (CH), 1728 (COO), 1231 (CO). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.43 (m, 3H), 7.25 – 7.09 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 2.22 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 183.0, 166.1, 159.2, 153.9, 140.6, 132.3, 130.5 (Cx2), 129.7, 127.1 (Cx2), 62.0, 25.1, 21.9, 14.0. LRMS (ESI^+) m/z 288, 288 [M] + 40%. HRMS (ES+) for $C_{15}H_{16}N_2O_2S$, calculated 289.1005, found 289.1004.; RP-HPLC Alltima™ C_{18} 5 µm 150 mm x 4.6 mm, 10-100% B in 15 min, R_t = 5.19 min, 100%.

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Supplementary Material

Supplementary material comprising full experimental detail, ^{1}H, ^{13}C NMR and LCMS evaluation of compounds **8a**-**8j** and **10a** and **10b** in PDF format is available as a separate electronic file.