

Pyrroloimidazolidiones derived from Aminomalonates and Benzaldehydes

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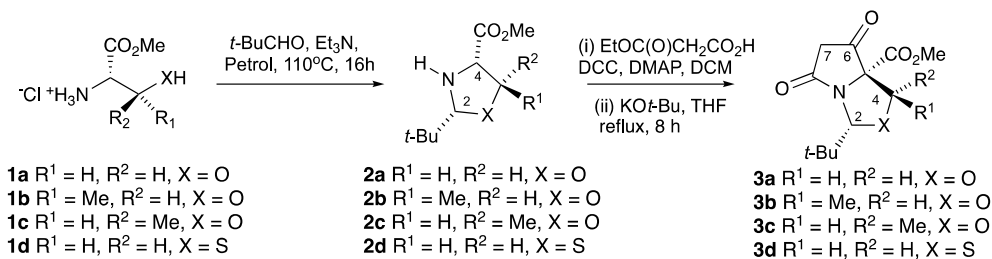
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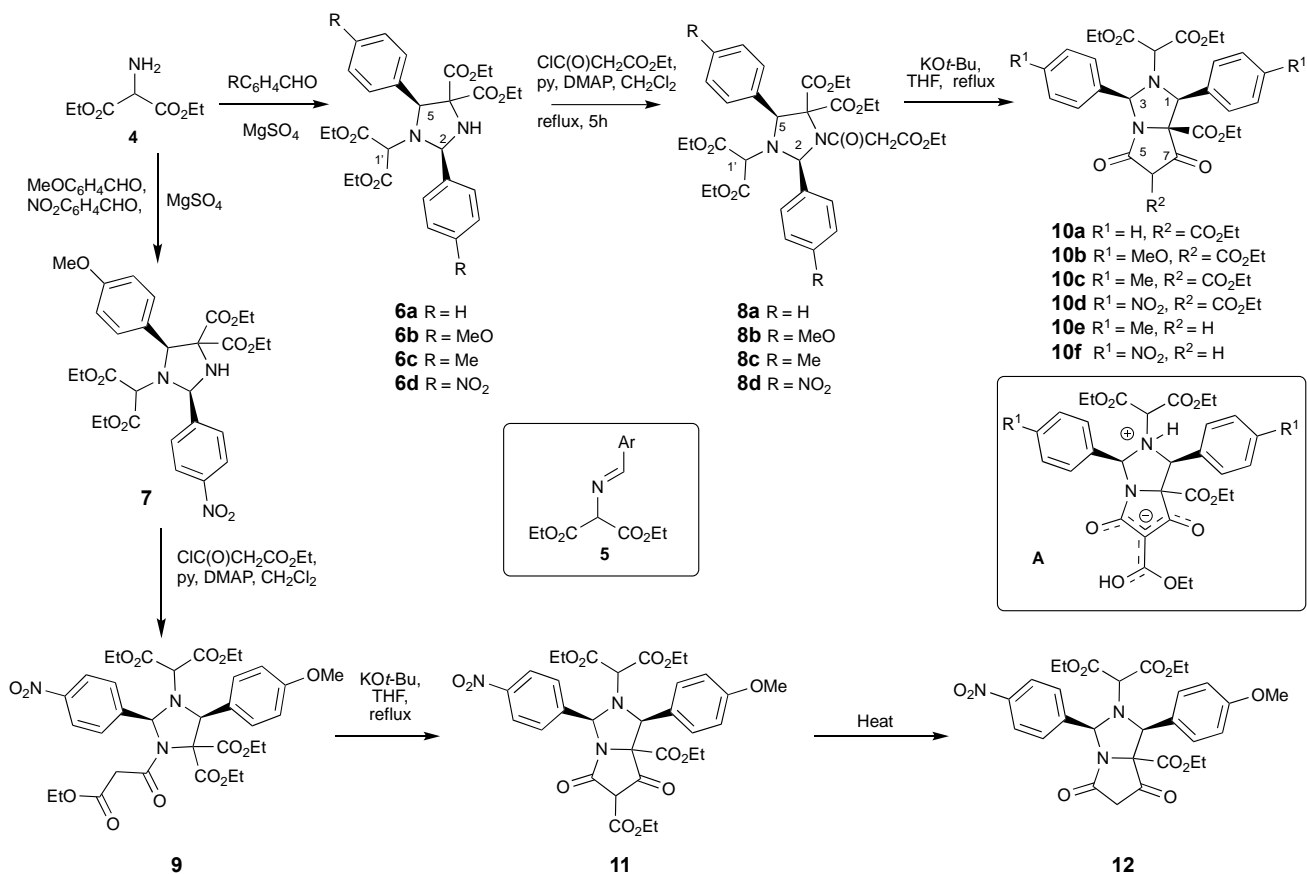
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Abstract: Bicyclic lactams may be prepared from amino diethylmalonate and substituted benzaldehydes by formation of a dimerised imidazolidine cycloadduct followed by Dieckmann ring closure; the resulting *N,N*-heterocycles are metal chelating but show no antibacterial activity.

We have shown that L-serine, L-cysteine, L-allothreonine and L-threonine methyl esters **1a-d** may be converted to their corresponding *O,N*- or *S,N*-hemiaminal ether or thioethers **2a-d** by condensation with aldehydes, and that these in turn may be converted to tetramates **3a-d** by a highly chemo- and enantioselective Dieckmann cyclisation (Scheme 1).^{1, 2} While oxazolidines and thiazolidines are stable,³ the possibility of forming the analogous a tetramate with an embedded imidazolidine was less certain, especially given the greater basicity of the nitrogen atoms and therefore potential for acid-mediated decomposition; the successful synthesis of tetramates incorporating such an *N,N*-heterocycle system is reported here. Application of the analogous process for the preparation of **2** (*X* = NR) would require β-aminoalanine, but since this is not readily available, an alternative strategy was required. Fortuitously, while investigating some earlier reported work,⁴ we found that the reaction of diethyl 2-aminomalonate (**4**) and benzaldehyde did not give diethyl 2-(benzylideneamino)malonate (**5**, Ar = Ph) as expected but instead imidazolidine **6a**,⁵ whose *cis*-diaryl arrangement was confirmed by NOE analysis and single crystal X-ray analysis (Figure 1).⁶ Such imidazolidines had previously reported under similar reaction conditions, as a result of rapid dipolar cycloaddition reactions of the intermediate aryl imine **5** (Scheme 1).^{7, 8}



Scheme 1



Scheme 2

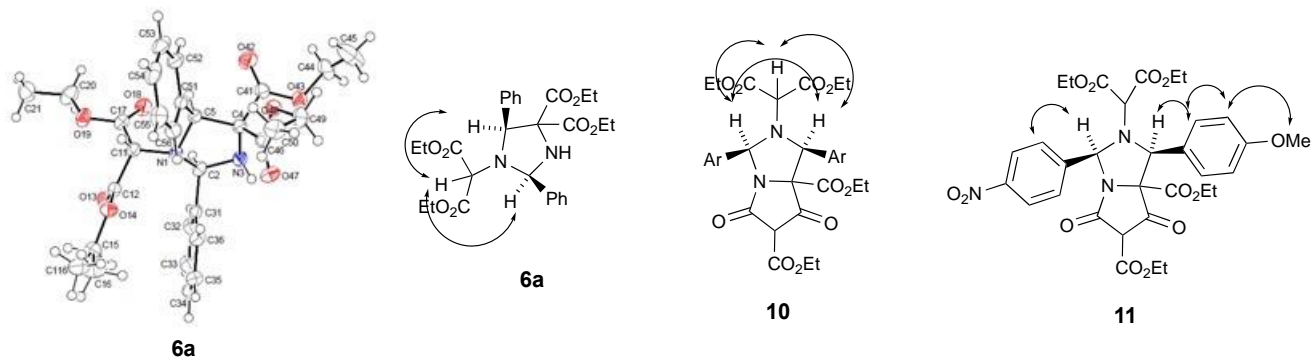


Figure 1

Since **6a** was effectively a derivative of the β -aminoalanine that was required, *p*-tolualdehyde, *p*-anisaldehyde and *p*-nitrobenzaldehyde were each used following the same procedure, all of which resulted in recovery of the desired imidazolidine products **6b-d** respectively in similar yields of up to

79% (Table 1). Compounds **6b** and **6d** had been previously reported but compound **6c** was novel.^{8, 9} Preservation of similar proton chemical shift values across the series of imidazolidine products suggested that these all possessed the same *cis*- orientation of the aryl groups, and this was confirmed by NOESY analysis of later tetramate products.

Table 1: Imidazolidine Compounds **6** and **7**.

Imidazolidine	Yield (%)	δ_{H} (ppm)				δ_{C} (ppm)		
		H2	H1'	H5	HN	C2	C1'	C5
6a	79	5.28	4.07	5.63	3.65	78.36	62.21	67.64
6b	68	5.21	4.03	5.51	3.51	77.67	61.95	67.07
6c	53	5.23	4.05	5.55	3.55	78.08	62.09	67.41
6d	63	5.41	3.99	5.72	3.55	77.74	62.09	67.33
7	50	5.45	4.03	5.49	3.51	77.23	61.39	68.09

Attempts were made to apply the reaction to two aldehydes of different reactivity, with the intention to obtain differently substituted systems (Scheme 2); for example, reaction with diethyl aminomalonate (1.0 equiv.), benzaldehyde (0.5 equiv.) and *p*-anisaldehyde (0.5 equiv.) did not give the desired mixed imidazolidine products, but instead only imidazolidine **6b**. A similar reaction using isobutyraldehyde (0.5 equiv.) gave the same outcome, and this is consistent with the absence of alkyl aldehyde-derived imidazolidines prepared via this methodology in reported work.^{7, 8} However, a reaction of *p*-anisaldehyde (0.5 equiv.) and *p*-nitrobenzaldehyde (0.5 equiv.) with diethyl aminomalonate (1.0 equiv.) did give the desired imidazolidine **7** as the major product (50% yield), although along with imidazolidine **6b**. Clean NMR spectra showing sharp singlets for key characteristic peaks indicated that a single structural isomer was formed, assigned as indicated in Table 1. The regiochemistry and *cis*-diaryl relationship was later confirmed by analysis of downstream products (see below).

If imidazolidine **6a** was refluxed in DCM with excess ethyl malonyl chloride, pyridine and 0.1 equivalents of DMAP,² the desired acylated product **8a** could be isolated in high yield (Table 2), characterised in the ¹H NMR spectrum by a pair of doublets at 2.56 and 2.92 ppm for the new malonyl CH₂ group.⁵ Application of these reaction conditions to *p*-methoxy and *p*-methyl imidazolidines (**6b** and **6c**) was also successful, resulting in isolable products **8b** and **8c**; these both displayed the characteristic pair of doublets seen in ¹H NMR at 2.57 and 2.93 ppm and at 2.56 and 2.93 ppm respectively. However, attempts to acylate the *p*-nitro compound **6d** and the mixed *p*-nitro/*p*-methoxy imidazolidine **7** did not give clean products **8d** and **9**, and although low resolution mass spectrometry

showed the expected molecular mass ions for the acylated material, NMR peaks were low and broadened. These compounds were instead used in crude form.

Table 2: Acylated Intermediates **8** and **9**

Acylated Intermediate	Yield (%)	δ_H (ppm)			δ_C (ppm)		
		H2	H1'	H5	C2	C3'	C5
8a	86	6.25	4.06	5.04	78.06	61.82	70.10
8b	70	6.24	4.06	4.89	77.33	61.37	69.67
8c	55	6.23	4.05	4.94	77.43	60.91	70.07
8d	Crude	-	-	-	-	-	-
9	Crude	-	-	-	-	-	-

Cyclisation of these derivatives was attempted using standard procedures for Dieckmann cyclisation,^{2, 10} which successfully gave the desired *N,N*-tetramate products **10** (Scheme 2) but in low yield. This outcome appeared to result from the difficulty of extraction of the product from the aqueous phase during the work up, rather than poor conversion of the starting material, since TLC analysis showed full consumption of **8a** over the course of the reaction. It was also noted that during column chromatography on silica, the desired product was very immobile and required a highly polar mobile phase of 10% methanol in ethyl acetate for elution. Moreover, following column chromatography, it was observed that ¹H NMR peaks were broad until the product was washed with 2M HCl, suggesting that the α,α,α -tricarbonyl substructure was chelating metal ions.¹¹ This has previously been observed with other tetramic acid derivatives which have proven to be non-selective but efficient chelators of a variety of metal ions.^{12, 13} Also worthy of note was the fact that although most of the characteristic protons appeared as sharp, clear singlets, no ¹H NMR signal was observed for the α,α,α -tricarbonyl proton H-7, and the absence of an OH signal implied a high proportion of enolisation.¹⁴ Moreover, it is likely that these products exist in zwitterionic form type A (Scheme 1), which would be highly polar and harder to extract from the aqueous phase, as observed during work-up.¹⁵ The other acylated intermediates **8b-d**, **9** all showed the same immobility on silica, the same peak broadening in ¹H NMR spectra before washing with HCl and the same absence of the H-7 peak in NMR spectrum. Whilst most of the yields are good, that of *p*-nitro/*p*-methoxy tetramate product **11** was poor (8%), also likely to have been the result of poor recovery rather than poor conversion; once again, TLC showed that all the starting material was consumed over the course of the reaction. NOESY analysis was used to confirm the *cis*- orientation of the aryl groups for all the products **10b-d**, and for compound **11** also allowed assignment of the relative positions of the *p*-methoxy and *p*-nitro aryl groups. NOE interactions between H-2, H-3' and H-4 were seen for all the tetramate products, and for compound

11, H-4 only showed interactions with aromatic protons from the *p*-methoxybenzyl group and H-2 showed interactions only with aromatic protons on the *p*-nitrobenzyl substituent (Figure 1). The relative configuration for **10a** was tentatively assigned as all *cis*-, since by calculation the indicated structure was more stable than the alternative epimer; this assignment could not be substantiated by NOE or X-ray analysis. The chemoselectivity and stereoselectivity of this outcome most likely arises as a result of thermodynamic control of the reaction, leading to the most stable outcome, a phenomenon which has been previously reported.¹⁶

Table 3: Tetramate Containing Products **10-12**

Tetramate	Yield(%)	δ_H (ppm)			δ_C (ppm)		
		H1	H1'	H3	C1	C1'	C4
10a	35	6.37	4.34	4.95	74.93	63.92	69.50
10b	41	6.24	4.28	4.83	74.78	62.22	68.39
10c	62	6.26	4.31	4.88	74.71	63.57	69.82
10d	26	6.38	4.30	5.07	73.33	63.29	69.30
10f	100	6.58	4.42	5.16	75.81	65.68	68.30
11	8	6.38	4.32	4.88	74.78	63.69	68.39
12	100	6.60	4.39	4.95	75.56	65.50	69.94

Over time, it was found that tetramates **10c** and **10d** in solution in CDCl₃ decayed by complete decarboxylation at the C-7 position, resulting in the products **10e** and **10f** (Table 3). When *p*-nitro/*p*-methoxy derivative **11**, in solution in CDCl₃, was heated to approximately 50°C for 24 hours, complete decarboxylation to **12** occurred; monitoring by NMR spectroscopy showed complete conversion after about 12h.

Of interest was further investigation of the metal chelating character of tetramates **10** and **12**, since this is a characteristic which is of some chemical and biological interest.^{12, 17} As has been noted above, after purification by silica column, the final tetramate products displayed broadened peaks in their ¹H NMR spectra until they were washed with 2M HCl. This was once again thought to be caused by the formation of chelates with metal ions present in silica gel. Bicyclic *N,O*-tetramic acid derivatives which also possess a similar tricarbonyl motif have previously been reported to display non-selective chelation ability and bind metal ions including Fe(III), Al(III), Cu(II), Mg(II) Ca(II) and Zn(II).^{12, 13} To test whether the *N,N*-tetramate derivatives behaved similarly, to DCM solutions of both **10a** and **10b**, 1M aqueous MgCl₂, Fe(SO₄) and Ca(NO₃)₂ solution were each added and the solution stirred for 1 hour. The organic phases were separated and the solvent evaporated, and then NMR

spectra were recorded of the residues. The ^1H NMR spectra (Figure 1, ESI) of the Ca^{2+} and Mg^{2+} samples showed noticeable broadening, similar to that observed during the original preparation of the tetramate products before they were washed with 2M HCl. This suggests that these compounds are readily capable of forming chelates with both Ca^{2+} and Mg^{2+} ions, and especially during column chromatography on silica, for which metal impurities have been reported.¹⁸ The Fe^{2+} experiment gave a deep red coloured solution and NMR spectra with paramagnetic broadening (Figure 1, ESI).¹⁹

The five different *N,N*-tetramates (**10a**, **11**, **10b**, **10c** and **10d**) showed no activity against *S. aureus* and *E.coli*, and this is in keeping with other unsubstituted tetramates as reported earlier.²⁰

Conclusion

We have shown that the efficient and rapid preparation of bicyclic *N,N*-tetramates starting from diethyl aminomalonate and a range of aromatic aldehydes is possible in three steps and in reasonable yields. These have been shown to reversibly form chelates with both Ca^{2+} and Mg^{2+} ions, present as impurities in silica gel used for column chromatography.

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5. **(±)-Diethyl (2R,5S)-1-(1,3-diethoxy-1,3-dioxopropan-2-yl)-2,5-diphenylimidazolidine-4,4-dicarboxylate 6a.** Diethyl aminomalonate (1000 mg, 5.71 mmol), benzaldehyde (606 mg, 5.71 mmol, 1.0 equiv) and MgSO_4 were added to dry DCM (20 ml) and refluxed for 16 hours. The reaction mixture was then filtered and the solvent evaporated to yield crude product. This was purified by column chromatography over silica, increasing polarity from 10 to 40% ethyl acetate in petrol. of the target product were isolated (1192.4 mg, 79%); **(±)-Diethyl (2S,5S)-1-(1,3-diethoxy-1,3-dioxopropan-2-yl)-3-(3-ethoxy-3-oxopropanoyl)-2,5-diphenylimidazolidine-4,4-dicarboxylate 8a.** **6a** (285.0 mg, 0.542 mmol) was dissolved in DCM (20 ml) with pyridine (85.4 mg, 1.08 mmol, 2.0 equiv) and DMAP (6.6 mg, 0.054 mmol, 0.1 equiv). This was stirred and cooled to 0°C. Ethyl malonyl chloride (163.1 mg, 1.084 mmol, 2.0 equiv) was also dissolved in DCM (5 ml) then added dropwise to the reaction mixture. The mixture was then stirred for a further 15 minutes at 0°C before being refluxed for 16 hours. At this point, the mixture was diluted with more DCM (30 ml), washed with saturated ammonium chloride solution (aq), then washed with 10% sodium hydrogen carbonate solution (aq) and finally with brine. The organic layers were dried with MgSO_4 then combined and

evaporated under vacuum. This gave crude product which was then purified by column chromatography over silica, with 20% ethyl acetate in petrol. The desired product was obtained as a pale oil (302 mg, 87%); (\pm)-Diethyl (1S, 3S)-2-(1,3-diethoxy-1,3-dioxopropan-2-yl)-5,7-dioxo-1,3-diphenyltetrahydro-1H-pyrrolo[1,2-c]imidazole-6,7a(5H)-dicarboxylate **10a**. **8a** (1195 mg, 1.86 mmol) was dissolved in dry THF (50 ml) with potassium tert-butoxide (220.0 mg, 1.05 equiv, 1.96 mmol). The mix was then refluxed for 16 hours. The crude mix was evaporated, then redissolved in diethyl ether (50 ml) and extracted with water (2 x 50 ml). The aqueous phase was then acidified with 2M HCl to pH 2 and extracted with ethyl acetate (3 x 100 ml). The organic phases were combined, dried over MgSO₄, and evaporated. This yielded crude product which was then purified by column over silica increasing polarity from 50% ethyl acetate in petrol to 10% methanol in ethyl acetate. The desired product was then washed twice with 2M HCl and once with saturated NH₄Cl (aq) to yield pure product (388.9 mg, 35%).

6. Low temperature single crystal X-ray diffraction data for **6a** were collected using a Rigaku Oxford SuperNova diffractometer. Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip' [L. Palatinus and G. Chapuis, *J. Appl. Cryst.*, **2007**, 40, 786-790.] before refinement with CRYSTALS [(a) P. Parois, R.I. Cooper and A.L. Thompson, *Chem. Cent. J.*, **2015**, 9:30. (b) R. I. Cooper, A. L. Thompson and D. J. Watkin, *J. Appl. Cryst.* **2010**, 43, 1100-1107.] as per the SI (CIF). Full refinement details are given in the Supporting Information (CIF); Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 2097494) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

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