

OXIDATION OF ENAMINE-ESTERS WITH LEAD TETRA-ACETATE—PART 3

β-AMINOCINNAMATES AND β-AMINOCROTONATES¹

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(Received in UK 30 March 1982)

Abstract—Oxidation of β-aminocinnamates and β-aminocrotonates with lead tetra-acetate gives fully substituted pyrrole-3, 4-diesters.

The synthesis of pyrroles of type 4 in one or two steps from α-aminoketones and dimethyl acetylenedicarboxylate involves aminofumarate esters (1) as intermediates, or the corresponding aminomaleates (3) in cases where the N atom is fully substituted.²⁻⁴ The aminofumarates (1; R² = Me, CH₂Ph, Ph) are oxidised by lead tetra-acetate (LTA) to give the corresponding pyrrole-tetraesters (5) and other heterocyclic products.^{1,5,6} A related enamine-ester, ethyl β-aminocrotonate (7g) is, probably an intermediate in the Hantzsch synthesis of pyrroles from ethyl acetoacetate, ammonia, and α-chloroketones.⁷ We report the results of LTA-oxidation of β-amino-crotonates and -cinnamates in extension of our previous work in this area.^{1,5}

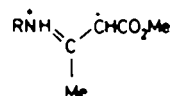
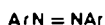
pyrroles (8a-e) in 20-40% yield. The symmetrical substitution pattern of these products was confirmed by their ¹H and ¹³C NMR spectra. Only 8a had been reported previously,⁹ but other pyrroles with the same substitution pattern (6; R² = H, Me, CH₂Ph) have been obtained by electrochemical oxidation of β-aminocrotonates (2)¹⁰ or via 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate to mesoionic oxazolones.¹¹ Trace amounts of the orange azobenzene derivatives (11a and b) were obtained from the oxidation of the anilincrotonates (7e and f), although in the latter case the corresponding pyrrole was not isolated.

The electrochemical oxidation of 2 is thought to involve dimerisation of radical cations (12).¹⁰ The same mechanism could apply to the LTA-oxidation, but it is more likely that the new C-C bond is made as a result of two-electron oxidation of the enamine as outlined in the Scheme. In either mechanism, the oxidative

RESULTS AND DISCUSSION

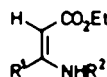
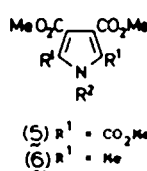
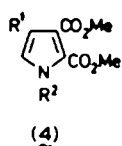
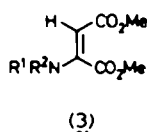
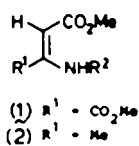
β-Ketoesters are ambident electrophiles for condensation with amines, but the greater reactivity of ketone than ester CO groups leads to the preferential formation of enamine-esters in most cases. We have employed the series of enamines (7 and 9), all of which possess the Z-configuration with an intramolecular H-bond, as indicated by the chemical shift of the NMR signal for the NH group below δ 8.5.¹

Oxidation of the aminocrotonates (7a-e) with an equimolar amount of LTA afforded the corresponding

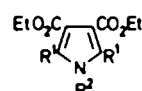


- (11) a; Ar = p-ClC₆H₄
 b; Ar = 3,5-xylyl

(12)



- a; R² = Me
 b; R² = Bu¹
 c; R² = PhCH₂
 d; R² = cyclo-C₇H₁₃
 e; R² = p-ClC₆H₄
 f; R² = 3,5-xylyl
 g; R² = H

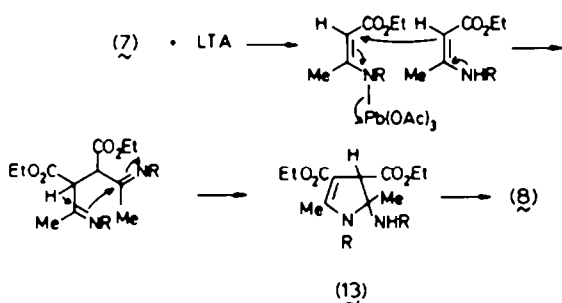


- a; R² = Me
 b; R² = Bu¹
 c; R² = PhCH₂
 d; R² = cyclo-C₇H₁₃
 e; R² = p-ClC₆H₄

- (9) R¹ = Ph
 a; R² = Me
 b; R² = Pr¹
 c; R² = PhCH₂
 d; R² = p-ClC₆H₄

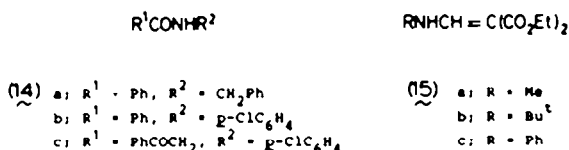
- (10) R¹ = Ph
 a; R² = Me
 b; R² = Pr¹
 c; R² = PhCH₂
 d; R² = p-ClC₆H₄

dimer must cyclise first to a pyrroline (13), which is deaminated to give the pyrrole (8). The corresponding pyrroline has been isolated from the I.TA-oxidation of dimethyl anilinoformate.¹ The azo compounds (11) may be formed by LTA-oxidation of primary aromatic amines eliminated in the last step;¹² primary aliphatic amines are oxidised to nitriles under similar conditions,¹³ and indeed benzonitrile was detected as a by-product from the oxidation of the *N*-benzylaminocrotonate (7c).



Scheme 1.

Oxidation of the β -aminocinnamates (9a-d) was less satisfactory. The corresponding pyrroles (10a-d) were obtained in 10–20% yield from reactions under N_2 , but with LTA in air the amides (14a and b) were obtained in low yield from the enamine-esters (9c and d), respectively. We have noted the similar oxidative cleavage of aminofumarates (1; $R^2 = p\text{-ClC}_6\text{H}_4$, $p\text{-MeCOC}_6\text{H}_4$, $p\text{-O}_2\text{NC}_6\text{H}_4$),¹ which appears to be autoxidation catalysed by lead(IV). Steric hindrance may impede the formation of pyrroles (10) with phenyl groups at the 2- and 5-positions. In spite of their structural resemblance to the enamine-esters (7 and 9), a series of aminomethylenemalonates (15a-c) were resistant to oxidation by I.TA.



These results extend the usefulness of enamine-esters for the synthesis of pyrrole derivatives. Oxidation with LTA gives results parallel to those from electrochemical oxidation of the same intermediates, but with the advantage of greater convenience.

EXPERIMENTAL

IR absorptions are quoted only for the regions 1600–1800 and 3000–3500 cm^{-1} . ^1H NMR spectra were obtained at 60 or 100 MHz (Varian EM360A or JEOL MH100 instruments) and ^{13}C NMR spectra at 15 MHz (JEOL FX60) for solns in CDCl_3 with TMS as internal standard. Mass spectra were obtained by electron impact at 70 eV (A.E.I. MS30); only those fragment ions with intensity > 25% of the base peak are listed.

Enamine-esters (7 and 9). Isobutylamine (5.5 g) and ethyl acetoacetate (10.0 g) in EtOH (20 ml) were heated at 35–40° for 3 hr. The solvent was evaporated and the residue distilled *in vacuo* to give ethyl *N*-isobutylaminocrotonate (7b) (12.3 g, 88%), b.p. 68–72° at 0.05 mmHg (Found: C, 64.9; H, 10.45; N, 7.4

$\text{C}_{10}\text{H}_{19}\text{NO}_2$ requires: C, 64.8; H, 10.3; N, 7.65%). ν_{max} 1610, 1655 ($\text{C}=\text{O}$) and 3290 ($\text{N}-\text{H}$) cm^{-1} ; 8.67 (1 H, br, NH), 4.42 (1 H, s, =CH), 4.07 (2 H, q, OCH_2), 3.02 (2 H, t, NCH₂), 1.88 (3 H, s, =CMe), 1.78 (1 H, m, tertiary CH), 1.23 (3 H, t, OCH_2Me), and 0.96 (6 H, d, CHMe_2), *m/e* 185 (M^+ , 15%), 142 (29), and 96 (100).

The same procedure using cycloheptylamine afforded ethyl *N*-cycloheptylaminocrotonate (7d; 82%) as an oil, b.p. 101–102° at 0.05 mmHg (Found: C, 69.2; H, 10.4; N, 6.2. $\text{C}_{11}\text{H}_{21}\text{NO}_2$ requires: C, 69.3; H, 10.3; N, 6.2%). ν_{max} 1610, 1653 ($\text{C}=\text{O}$) and 3280 ($\text{N}-\text{H}$) cm^{-1} ; 8.76 (1 H, br, NH), 4.41 (1 H, s, =CH), 4.10 (2 H, q, OCH_2), 3.58 (1 H, m, NCH), 1.92 (3 H, s, =CMe), 1.3–2.0 (12 H, m, ring CH_2), and 1.24 (3 H, t, CH_2Me), *m/e* 225 (M^+ , 82%), 130 (100), and 122 (28).

The same procedure using methylamine or benzylamine gave 7a, b.p. 62–64° at 0.15 mmHg (lit.¹⁴ b.p. 133° at 50 mmHg), and 7c, m.p. 84–87° (lit.¹⁴ 79–80°); ^1H NMR spectra very similar to those above, except for absorptions appropriate to the *N*-substituent.

Compound 7e, m.p. 52–54° (lit.¹⁵ 55°), was prepared by heating *p*-chloroaniline and ethyl acetoacetate in benzene containing AcOH and azeotropic removal of water in a Dean-Stark trap. In the same way 3, 5-xylidine (6.1 g) and ethyl acetoacetate (6.5 g) in benzene (50 ml) containing AcOH (1 ml) were heated under reflux until the calculated amount of water (0.9 ml) was collected. The solvent was evaporated and the residue distilled to give ethyl 3, 5-xylidinocrotonate (7f; 11.7 g, 79%) as an oil, b.p. 112–118° at 0.1 mmHg (Found: C, 72.3; H, 8.2; N, 5.9. $\text{C}_{14}\text{H}_{19}\text{NO}_2$ requires: C, 72.1; H, 8.2; N, 6.0%). ν_{max} (CHCl_3) 1650 ($\text{C}=\text{O}$) and 3280 ($\text{N}-\text{H}$) cm^{-1} ; 8.10.48 (1 H, br, NH), 6.93 and 6.86 (1 H and 2 H, respectively, s, ArH), 4.76 (1 H, s, =CH), 4.24 (2 H, q, OCH_2), 2.33 (6 H, s, ArMe), 2.01 (3 H, s, =CMe), and 1.29 (3 H, t, CH_2Me), *m/e* 233 (M^+ , 16%), 121 (100), and 120 (40).

9a, b.p. 102–105° at 0.4 mmHg (lit.¹⁴ b.p. 130–134° at 2 mmHg) and 9b, b.p. 113–114.5° at 0.05 mmHg (lit.¹⁶ b.p. 170–173° at 4–5 mmHg) were obtained by heating the appropriate amine with ethyl benzoylacetate in refluxing EtOH, followed by fractional distillation *in vacuo*. 9c, m.p. 72–73.5° (lit.¹⁶ 68–69°), was obtained in the same way, but using *n*-propanol as the solvent and recrystallisation of the residue left after evaporation of solvent.

p-Chloroaniline (12.8 g) and ethyl benzoylacetate (19.2 g) in benzene (50 ml) containing *p*-toluenesulphonic acid (0.4 g) were heated under reflux for 5 hr with removal of water in a Dean-Stark trap. The first crop of solid which was deposited as the mixture cooled to room temp was collected and recrystallised to give 14c (4.2 g, 15%), m.p. 158–159° (lit.¹⁷ 157–158°). The mother liquor was concentrated and chilled overnight to afford a second crop of solid, which was collected and recrystallised to give 9d (9.2 g, 31%), m.p. 111–114° (lit.¹⁷ 111–113°).

Oxidations with LTA. LTA was recrystallised from AcOH, washed with CCl_4 , and stored in a vacuum desiccator prior to use. LTA (4.5 g, 10 mmol) was added to the 7 (10 mmol) in CH_2Cl_2 (40 ml) and the mixture allowed to stand for 3–7 hr. After testing for the absence of unreacted lead(IV), the mixture was extracted with water to remove lead diacetate, the organic layer was retained, washed with NaHCO_3 aq and with water, dried with MgSO_4 , and rotary-evaporated to remove solvent. The residue then afforded 8 listed in Table 1, of which 8a was obtained directly by recrystallisation and 8b–e after chromatography on alumina or silica gel. ^1H NMR data are summarised in Table 2, and ^{13}C NMR spectra of 8b–e were closely similar to that of 8a, δ , 165.6 ($\text{C}=\text{O}$), 133.3 and 111.7 (pyrrole ring carbons), 59.9 and 14.1 (OEt), 30.2 (NMe), and 10.8 (CMe), apart from other absorptions appropriate to the *N*-substituent. Mass spectra of 8a–e showed the correct molecular ion in each case and fragmentation involving the CO_2Et group. Yields were not systematically optimised. A slightly higher yield (39%) of 8c in another experiment using a 0.5:1 mole ratio of LTA:enamine (7c) is of doubtful significance in view of the observation that 8c is unaffected by LTA under the same conditions.

Benzonitrile was identified (GC retention time and GC-MS) as a trace component of the crude product mixture from oxidation of 7c. The crude product obtained from LTA-oxidation of 7e also afforded 11a (5 mg), orange needles, m.p. 188° (lit.¹⁸ 187.5–188.5°), eluted from silica gel with light petroleum-ether (4:1 v/v) before

Table 1. Characterisation of pyrroles (8) and (10)

Compound	Yield (%)	m.p. (°C)	Found (%)			Formula	Requires (%)		
			C	H	N		C	H	N
(8a)	41	71 - 72 ^a	61.5	7.6	5.6	C ₁₃ H ₁₉ NO ₄	61.6	7.6	5.5
(8b)	20	52 - 53.5	65.1	8.6	4.8	C ₁₆ H ₂₅ NO ₄	65.1	8.5	4.7
(8c)	34	61.5 - 63	69.0	7.2	4.3	C ₁₉ H ₂₃ NO ₄	69.3	7.0	4.3
(8d)	22	65 - 67	68.1	8.7	3.9	C ₁₉ H ₂₃ NO ₄	68.0	8.7	4.2
(8e)	20	98 - 99.5	61.8	5.6	4.1	C ₁₈ H ₂₀ CINO ₄	61.8	5.8	4.0
(10a)	14 ^b	125 - 126.5	73.1	6.3	3.7	C ₂₃ H ₂₃ NO ₄	73.2	6.1	3.7
(10b)	18 ^b	91.5 - 93	73.8	6.7	3.5	C ₂₅ H ₂₇ NO ₄	74.1	6.7	3.5
(10c)	12 ^b	120 - 121.5	77.1	6.3	3.1	C ₂₉ H ₂₇ NO ₄	76.8	6.0	3.1
(10d)	11 ^b	175 - 177	71.1	5.0	2.9	C ₂₈ H ₂₄ CINO ₄	71.0	5.1	3.0

^a Lit.⁹ m.p. 72 °C.^b Reaction under nitrogen (see text).Table 2. ¹H NMR data for pyrroles (8) and (10)^a

Compound	ArH	OCH ₂ ·CH ₃	-CCH ₃	NR
(8a)	-	4.24 (q), 1.30 (t)	2.33 (s)	3.35 (s, CH ₃)
(8b)	-	4.28 (q), 1.32 (t)	2.37 (s)	3.59 (d, CH ₂), 1.9-2.2 (m, CH), 0.92 (d, CH ₃)
(8c)	6.85-7.35 (m)	4.26 (q), 1.30 (t)	2.29 (s)	5.02 (s, CH ₂) and ArH
(8d)	-	4.22 (q), 1.30 (t)	2.42 (s)	4.1br (m, CH), 1.5-2.1br (m, CH ₂)
(8e)	-	4.22 (q), 1.31 (t)	2.10 (s)	6.98 and 7.36 (d, AA'BB' pattern)
(10a)	7.56 (s)	4.27 (q), 1.18 (t)	-	3.36 (s, CH ₃)
(10b)	7.41 (s)	4.08 (q), 1.07 (t)	-	3.63 (t, CH ₂), 2.2br (m, CH ₂), 0.44 (t, CH ₃)
(10c)	6.4-7.7 (m), 7.30 (s)	4.08 (q), 1.05 (t)	-	4.87 (s, CH ₂) and ArH
(10d)	7.13 (s)	4.12 (q), 1.13 (t)	-	6.70 and 6.98 (d, AA'BB' pattern)

^a Chemical shifts are quoted in p.p.m. downfield of tetramethylsilane as internal standard.

8e, identical (mixed m.p., IR and mass spectra) with an authentic sample prepared by LTA-oxidation of *p*-chloroaniline.¹² The crude product from LTA-oxidation of 7f similarly afforded the corresponding 11b (6 mg), m.p. 138-141° (lit.¹⁹ 136-137°), but further elution of the column gave no other crystalline material.

Compounds 9 were oxidised with LTA by the same procedure, but under N₂ and for longer reaction times (18 hr in the case of 9c and d). The crude product from 9a was triturated with MeOH and chilled to obtain 10a; in other cases the crude product was chromatographed to isolate 10b-d, which were characterised by data in Tables 1 and 2. The ¹³C NMR spectrum of 10a, δ, 164.8 (C=O), 136.6 and 114.4 (pyrrole ring carbons), 130.8, 130.4, 128.6, and 128.2 (benzene ring carbons), 60.2 and 13.9 (OEt), and 33.2 (NMe), is typical for 10a-d except for absorptions characteristic of the different N-substituents. The mass spectra of 10a-d showed the correct molecular ion in each case.

LTA-oxidation of 9c in air followed by chromatography of the crude product afforded unreacted 9c (6%), eluted with ether, followed by 14a (45 mg, 2%), m.p. 100-103.5° (lit.²⁰ 105°), eluted with CH₂Cl₂, identical with an authentic specimen. Similarly LTA-oxidation of 9d in air followed by chromatography afforded only 14b (62 mg, 3%), m.p. 191-193.5° (lit.²¹ 191-193°). In spite of low yields of 14a and b, 10c and d were not isolated.

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