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The Lead Tetra-acetate Oxidations of Some *N*-Arylaminofumarates in the Presence of Trifluoroacetic Acid

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ABSTRAK

p-Kloroanilino-, p-asetilanilino-, dan p-toluidino-fumarat telah dioksidakan oleh plumbum tetra-asetat untuk memberikan oksanilat dalam hasil yang rendah. Pengoksidaan yang serupa terhadap p-asetilanilinofumarat dengan adanya asid trifluoroasetik memberikan hanya oksanilat. p-Toluidino dan p-kloroanilino-fumarat oleh plumbum tetra-asetat/asid trifluoroasetik menghasilkan campuran oksazin, azobenzena dan anilida.

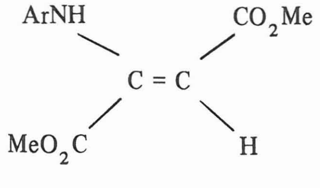
ABSTRACT

p-Chloroanilino-, p-acetylanilino-, and p-toluidino-fumarates are oxidized by lead tetra-acetate in low yields to give oxanilate. Similar oxidation of p-acetylanilinofumarate in the presence of trifluoroacetic acid affords only oxanilate. p-Toluidino and p-chloroanilino-fumarates with lead tetra-acetate/trifluoroacetic acid give mixtures of oxazin, azobenzene and anilide.

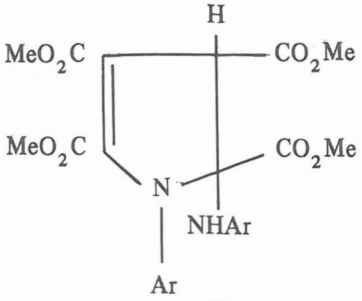
INTRODUCTION

Lead tetra-acetate (LTA) is an important and versatile oxidising agent and has been used to oxidize representatives of almost every class of organic compounds (Butler, 1977). Previous work on LTA oxidations of some nitrogen-containing compounds have been reported. Heterocyclic products, acyclic oxidative dimers, and oxanilates were obtained from the oxidations of some *N*-alkyl-and *N*-aryl-aminofumarates (Carr *et al.*, 1980; Vernon *et al.*, 1982; Sukari and Vernon, 1983). Oxidations of some 1, 2-disubstituted indoles afforded the corresponding 3-acetoxy derivatives which gave dioxindoles on heating with alkali (Sukari and Vernon, 1983).

In most cases, LTA is employed in a variety of solvents such as dichloromethane, benzene, acetonitrile, and chloroform. In the presence of trifluoroacetic acid (TFA) ligand exchange occurs to give lead tetrakistrifluoroacetate, $Pb(OCOCF_3)_4$, which is an even more powerful oxidant (Norman and Poustie, 1969). The work mentioned in this paper describes the LTA oxidations of some *N*-arylaminofumarates in the absence and in the presence of TFA.



(1) a: Ar = Ph
b: Ar = 3, $5\text{-}Me_2C_6H_3$
c: Ar = $P\text{–}O_2NC_6H_4$
d: Ar = $p\text{–}ClC_6H_4$
e: Ar = $p\text{–}MeCOC_6H_4$
f: Ar = $p\text{–}MeC_6H_4$



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MATERIAL AND METHODS

Instruments

Infra-red (IR) absorptions were recorded for Nujol mulls on a Pye Unicam SP 200 Spectrophotometer and quoted only for the regions 1600 – 1800 and 3000 – 3500 cm $^{-1}$. ^{1}H Nuclear magnetic resonance (NMR) spectra were obtained from Perkin-Elmer R10 and BRUKER WP 80 instruments. Solutions were generally in deuterated chloroform with tetramethylsilane (σ 0.0) as the internal standard. Mass spectra (MS) were obtained by electron impact at 70 eV(A.E.1. MS 30 instrument); only those fragment ions with an intensity of 20% of the base peak are reported.

Preparations of Aminofumarates

Dimethyl *N*-arylaminofumarates were prepared by Michael addition of the appropriate primary amines to dimethyl acetylenedicarboxylate and characterized by microanalysis and spectroscopic data (Vernon *et al.*, 1982).

Oxidations of Aminofumarates

LTA was freshly recrystallized from acetic acid, washed with carbon tetrachloride and dried before being used. The general procedure of oxidation involved addition of LTA to the fumarate, both in dry dichloromethane. The mixture was stirred, the unreacted LTA was destroyed by dropwise addition of ethane-1, 2-diol, and the by-product lead diacetate was removed by filtration. The filtrate was washed with water, then with aqueous sodium bicarbonate, dried with anhydrous magnesium sulphate, filtered, and the solvent was removed on the rotary evaporator.

Melting points were measured on a Kofler micro-heating stage, or on an Electrothermal m.p. apparatus and were uncorrected.

Oxidation of Dimethyl P-Chloroanilinofumarate (ld)

The fumarate (ld) (2.69 g) was oxidised with LTA (4.43 g) in dichloromethane (40 ml) at reflux temperature for 20 hours. The mixture was then cooled and work-up procedure gave an oil, which was chromatographed on silica-gel to give *methyl p-chlorooxanilate* (3: R = Cl) (55 mg, 2.5%) m.p. 168 – 169°C (from methanol), identical (IR Spectrum) with the authentic sample (Vernon *et al.*, 1982).

Fumarate (ld) (2.7 g) in dichloromethane (20 ml) was reacted with LTA (4.43 g) in dichloromethane (20 ml) and TFA (1.2 g) at reflux temperature for 18 hours. Work-up procedure was followed by chromatography on silica-gel. Elution with light petroleum-ether (4: 1 v/v) gave yellow crystals of the *1, 4-benzoxazin-2-one* (6: R = Cl) (57 mg, 2.3%), m.p. 183 – 185°C (from n-butanol). IR ν_{max} 1640, 1675, 1775 (C = 0) cm $^{-1}$. ^{1}*H NMR* (in DMSO-d$_6$) δ 9.38 (1H, s, NH), 7.56 – 7.10 (3H, m, ArH), 5.61 (1H, s, vinylic), 3.71 (3H, s, OMe). ^{13}*C NMR* (in DMSO-d$_6$) δ C 168.1 155.3 (C = 0); 140.2, 88.6 (C = C); 138.1, 125.3, 124.7, 123.8, 117.0, 116.1 (aromatic), 51.0 (OMe). *MS* m/e 255/253 (M $^+$, 15/43%), 223/221 (*M* $^+$ –MeOH, 34/100), 195/193 (29/81), 168/166 (10/27), 139/137 (19/52), 102 (44).

Elution with ether-dichloromethane (9: 1 v/v) yielded another product of unknown structure (25 mg), probably a dimer, m.p. 140 – 142°C (from methanol). IR ν_{max} 1650, 1725, 1765, 1780, (C = 0) cm $^{-1}$. *^{1}H NMR* 7.43 and 7.22 (each 2H, d, ArH), 3.87 and 3.79 (each 6H, s, OMe). *MS* m/e 427/425 (M^+, 14/42%), 383/381 (10/29), 367/365 (7/21), 340/338 (8/25), 162 (22), 111 (100), 75 (80).

The reaction of fumarate (ld) (5.4 g) with LTA (8.9 g) and TFA (2.5 g) was repeated in dichloromethane (50 ml) at reflux temperature overnight. Work-up procedure gave a mixture which was chromatographed on silica-gel. Light petroleum-ether (4: 1 v/v) eluted *compound (6: R = Cl)* (95 mg 1.9%) and *p, p'-dichloroazobenzene* (7), orange crystals (9 mg), m.p. 190.5 – 192.5°C (from chloroform) (Curtius and Raschig, 1930; m.p. 188°C), which was shown by mixed m.p. and IR spectrum to be identical with an authentic sample prepared from LTA oxidation of *p*-chloroaniline *^{1}H NMR* δ 7.86 and 7.52 (each 2H, dd, ArH). *MS* m/e (254/252/250 (M^+, 3/23/34%), 141/139 (p-ClC$_6$H$_4$N$_2^+$, 12/39), 113/111 (p-ClC$_6$H$_4^+$, 32/100), 75 (31).

In a separate experiment, the enamine (ld) (4.05 g) in dichloromethane (15 ml) was oxidized with LTA (6.0 g) in dichloromethane (20 ml) and TFA (5.55 g) at reflux temperature for 1 hour. The mixture was allowed to reach room temperature and put aside overnight. After work-up procedure, the product was chromatographed over silica-gel. Elution with light petroleum-ether (4: 1 v/v) yielded *p-p'*-dichloroazobenzene (7) (trace amount) and *trifluoroacetanilide* (8) (102 mg, 3%), m.p. 121 – 122°C (from chloroform-light petroleum), (Burns *et al.*, 1928; m.p. 122 – 123°C). IR ν_{max} 1620, 1715, 1735 (C = 0), 3320 (N-H) cm $^{-1}$. ^{1}H NMR δ 7.96 (1H, br, NH), 7.53 and 7.39 (each 2H, dd, ArH). *MS* m/e 225/223 (M^+, 29/100%) 156/154 (M^+-CF$_3$, 17/52), 128/126 (38/75), 101/99 (10/27), 63 (20).

Dimethyl *p*-chloroanilinofumarate (ld) (1.0 g) was mixed with TFA (2.1 g) in dichloromethane (10 ml) and heated under reflux for 1 hour, then left at room temperature overnight. The solution was concentrated and the solid that appeared was filtered to give *p*-chloroanilinium trifluoacetate (0.52 g), water soluble, m.p. 136 – 138°C (from chloroform-methanol). Some of the solid was dissolved in water, basified with NaOH solution, and extracted with ether. The ether was removed to give *p*-chloroaniline. Addition of TFA to *p*-chloroaniline in chloroform caused immediate precipitation of a white solid, which was found to be identical (IR spectrum) with the above product.

Oxidation of Dimethyl p-acetylanilinofumarate (le)

Fumarate (le) (2.76 g) and LTA (6.72 g) were reacted for 2 hours at room temperature, then for 1 hour at reflux temperature, and then to stand for 18 hours before work-up. The crude oil obtained was chromatographed over silica-gel, from which dichloromethena-methonal (9: 1 v/v) afforded *methyl P-acetyloxanilate* (3: R = MeCO) (0.12 g, 5%); m.p. 158 – 159°C (from methanol), identical (IR, NMR, MS and mixed m.p.) with the authentic sample (Vernon *et al.*, 1982).

The reaction of (le) (2.06 g) with equimolar amounts of LTA (4.43 g) and TFA (1.2 g) in dichloromethane at reflux temperature overnight gave, after being chromatographed over silica-gel, only the oxanilate (3: R = MeCO) (45 mg, 1.6%).

Oxidation of Dimethyl p-toluidinofumarate (lf)

The fumarate (lf) (2.5 g) in dichloromethane (10 ml) was reacted with LTA (6.7 g) in dichloromethane (20 ml) at room temperature for 20 hours, and all Pb(IV) was consumed. Work-up procedure followed by column chromatography over silica-gel elution with ether gave *methyl p-methyloxanilate* (3: R = Me) (17 mg, 0.9%), m.p. 146 – 149°C (from methanol) (Beilstein "Handbuch der Organischem Chem", Vol. 12; m.p. 145°C), which was shown by t.l.c. and mixed m.p. to be identical with an authentic sample.

Fumarate (lf) (2.1 g) in dichlorimethane (10 ml) was treated with LTA (4.43 g) in dichloromethane (15 ml) in the presence of TFA (1.2 g) at reflux temperature overnight. After work-up the crude product was chromatographed on silica-gel, from which light petroleum ether (4: 1 v/v) eluted the *compound (6: R = Me)* (17 mg, 0.9%), m.p. 168 – 172°C (from methanol). ^{1}*H NMR* δ 9.44 (1H, br, NH), 7.15 – 6.80 (3H, m, ArH), 5.84 (1H, s, vinylic), 3.73 (3H, s, OMe), 2.30 (3H, s, OMe). *MS* m/e 233 (M^+, 45%), 201 (M^+ -MeOH, 80), 174 (M^+ -CO$_2$Me, 21), 173 (100), 172 (27), 146 (23), 117 (43), 78 (53), 77 (40); *m** 173 (233 ⟶ 201).

RESULTS AND DISCUSSION

The pyrrolines (2) (Ar = Ph; 3, 5-Me$_2$C$_6$H$_3$) were isolated from the LTA oxidations of the corresponding fumarate (1) (Vernon *et al.*, 1982); Sukari and Vernon, 1984), whereas fumarate (1c) afforded the oxanilate (3) (R = NO$_2$) in low yield (Vernon *et al.*, 1982).

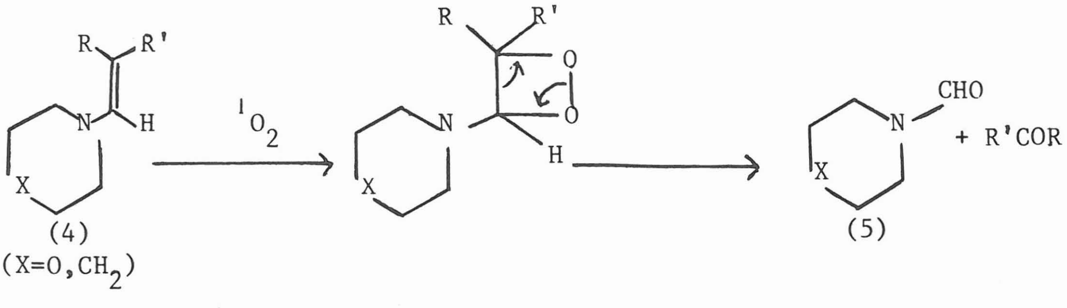
The enamine (1d and 1e) with electron withdrawing *para* substituents were noticeably less reactive than (1a) and (1b). Each of the compound (1d) and (1e) was reacted with equimolar quantity of LTA and the crude oily product mixture was chromatographed to give small amounts of unreacted enamine (<10%) and of solid products (<5%). Both products were recognised as the corresponding oxanilate (3) (R = *p*-ClC$_6$H$_4$, *p*-MeCOC$_6$H$_4$) on the basis of IR and NMR spectroscopic evidence. Authentic samples were prepared independently by the reaction of dimethyl oxalate and the appropriate amines (Vernon *et al.*, 1982).

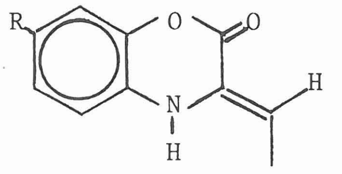
Dimethyl *p*-toluidinofumarate (If), with an electron-donating group at the *para*-position, was expected to behave the fumarates (1a) and (1b). However, oxidation of (If) with an equimolar amount of LTA in dichloromethane at reflux temperature did not give the corresponding pyrroline. Only methyl *p*-methyloxanilate (3: R = Me) was isolated in 1% yield. Melting point and spectra of this product were compared with those of an authentic sample obtained from *p*-toluidine and dimethyl oxalate. Formation of the oxanilate is an autoxidative cleavage, catalysed by lead (IV) (Vernon, Carr and Sukari, 1982). On the other hand, it resembles the cleavage of some other enamines on photosensitized oxygenation, such as piperidino and morpholino derivatives (4) which were oxidized to formamide (5) *via* decomposition of dioxtane intermediate *(Scheme 1)* (Foote and Lin, 1968; Adam, 1977).

Scheme 1

No trace of oxanilate was found from the LTA oxidation of (1a) and (b), in which pyrroline (2) was the only identifiable solid product. There was no obvious reason by oxidation of (1a) and (1b) gave pyrroline (2), whereas similar oxidation of the less reactive enamines (1c) – (1e) afforded the corresponding oxanilate (3).

The oxidation of fumarates (1d) – (1f) was also carried out in the presence of TFA. Fumarate (1e) with equimolar amounts of LTA and TFA in refluxing dichloromethane gave only the oxanilate (3: R = MeCO). Fumarates (1d) and (1f) under the same conditions yielded other products.





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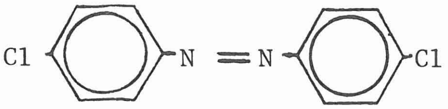

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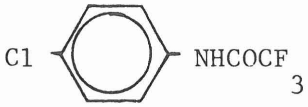

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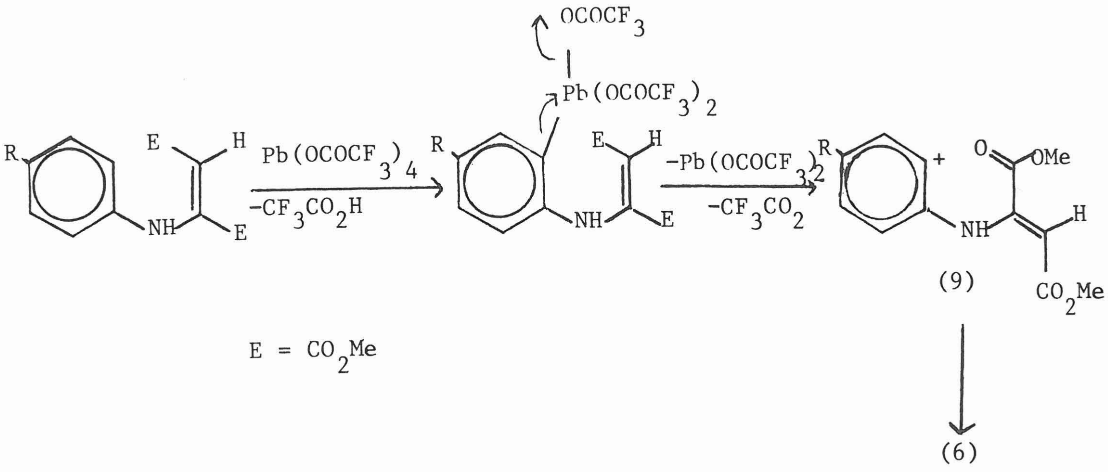
A product obtained from dimethyl *p*-toluidinofumarate (1f) had the molecular formula $C_{12}H_{11}NO_4$ from mass spectrometry. Dimethyl *p*-chloroanilinofumarate (1d) afforded a product $C_{11}H_8ClNO_4$ of the type. ^1H NMR spectra of both products showed appropriate resonances of the aryl, NH, vinylic CH, and OMe groups, which are consistent with the assignment of structures (6) (R = Me, Cl). The position of the NH resonance at low field suggests that there is hydrogen bonding between NH and ester groups. Compound (6) can be formed probably *via* the intermediate (9) obtained by attack of lead tetrakistrifluoroacetate on the corresponding fumarate *(Scheme 2)* (Partch, 1967).

Scheme 2

A second product from LTA oxidation of (1d) in the presence of TFA was isolated on only one occasion and was not fully characterized. The product gives the conflicting NMR and MS date and therefore does not allow the assignment of its structure.

Oxidation of fumarate (1d) also yielded trace amounts of an orange material, which was identified as *p,p'*-dichloroazobenze (7) on the basis of its ^1H NMR and MS. The identification was confirmed by comparison with an authentic sample obtained by LTA oxidation of *p*-chloroaniline (Baer and Tosani, 1956).



The LTA oxidation of (1d) in the presence of a three-fold amount of TFA afforded the azobenze (7) and another product, $C_8H_5ClF_3NO$. The latter was identified as the trifluoroacetanilide (8) from its melting point and IR absorption for NH and C = O groups. The isolation of these products suggests that TFA cleaves the fumarate (1d) to *p*-chloroaniline, from which both (7) and (8) are derived. The LTA oxidation of aromatic primary amines is well known and produces symmetrical azo-compounds, probably through the formation of intermediate hydrazo compounds (Pausacker and Scroggie, 1954; Baer and Tosoni, 1956).

A control experiment demonstrated that treatment of (ld) with TFA gave the salt, $p\text{-ClC}_6H_4NH_3^+ \; CF_3CO_2^-$, which was also obtainable from the reaction of *p*-chloroaniline with TFA.

All of the solid products mentioned above were isolated in the yield range of 1 – 5%. No effort has been made to separate or characterize any liquid product. In most cases the enamine starting material was recovered unchanged (< 10%) at the end of the reaction.

Unfortunately the preparative usefulness of these reaction is restricted by the low yields of the products. However, the variety of the products obtained is of interest in relation to the work reported previously.

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