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Alkylation with Oxalic Esters. Scope and Mechanism.

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Abstract: Alkyl oxalates are well suited for use as standard synthetic reagents in N–, O-, or S-alkylations and often display an interesting regioselectivity. The mechanism seems to be a direct alkylation of the substrate anion.

Introduction

The alkylating properties of oxalic esters have been known at least since 1960, when Sakakibara alkylated phenols at high temperatures.[1,2] A few more cases can be found in the literature,[3-6] but no systematic studies have been made to explore the use of oxalates as standard synthetic reagents. This can be attributed partly to the reaction temperature and the basic conditions which makes them unsuitable for sensitive substrates, and also because it does not appear to present much of a mechanistic challenge, *ie* it seems to be a textbook example of an S_N2-reaction. In a semi-empirical quantum chemical study we have used this as a probe for criticism of the Frontier Molecular Orbital (FMO) theory and obtained support for the expected S_N2-mechanism.[7]

Qing-Hua *et al*[5] observed that dimethyl oxalate is considerably less toxic than traditional methylating agents. It should therefore be very well suited to large-scale methylations. This fact, together with promising results from our initial study,[8] lead us to investigate the scope and mechanism of the reaction more closely.

Results and Discussion

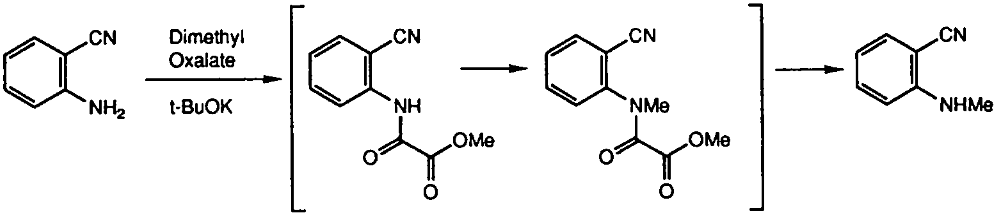
The results of the alkylations using dimethyl, diethyl, di-*sec*-butyl and dibenzyl oxalate are summarized in Table I. When the substrate has more than one nucleophilic center, the position of alkylation is indicated.

Alkylation of *o*-mercaptoaniline yields the *S*-alkylated product, as expected. Methylation of 4–nitroimidazole gives an easily purified isomeric mixture, where the 1-alkyl-4-nitro isomer dominates in a ratio of 4 to 1, as determined by ^1H NMR. As a comparison, it has been shown that dimethyl sulfate reacts with 4-nitroimidazole in acidic media to give mainly the 1-alkyl-5-nitro isomer in an isomeric ratio of 350:1.[9a] In basic solutions the reaction yields mainly the 1-alkyl-4-nitro product (ratio 3:1).[9b]

Indoles are strongly nucleophilic in the 3-position, and many alkylating agents will alkylate indoles at that site. Oxalic esters selectively monoalkylate various indoles at the 1-nitrogen. Purines were monomethylated at the 9-position.

Methylation of benzotriazole yielded a mixture of 1- and 2-methyl benzotriazole (ratio 2:1). This is to be expected from alkylation of benzotriazole under alkaline conditions, although other alkylating methods may give widely differing ratios.[10]

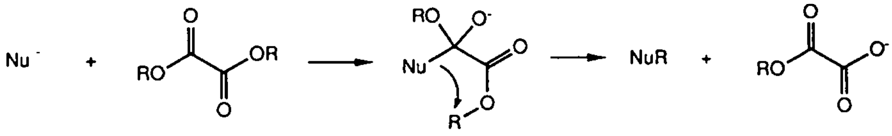
Anthranilonitrile, a primary amine, has been monomethylated in good yield.[11] The mechanism in this case seems to involve the alkylation of an intermediate oxalamide, and subsequent cleavage to the monoalkylated amine (Scheme 1). The intermediates have been independently prepared and subjected to the reaction conditions, in all cases yielding the expected *N*–methylanthranilonitrile.[11]



Scheme 1

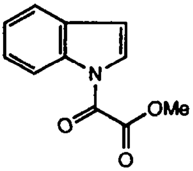
Lespagnol[3] has shown that phenothiazine is alkylated by oxalate in neutral and acidic media, but the substrates in our study gave only low yields of acylated products in the absence of a base strong enough to deprotonate the substrate.

It can be argued that all alkylations proceed *via* acylated intermediates, as shown in Scheme 2.



Scheme 2

In order to test this, two acylated indoles, namely methyl 1-oxo-1-(*N*–indolyl)-acetate (**1**) and ethyl 1-oxo-1-(*N*–indolyl)-acetate (**2**) were prepared by dehydrogenation of the corresponding indolines.[12]



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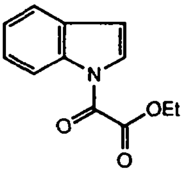

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If **1** or **2** were intermediates in the alkylation reaction, then reflux with potassium *t*–butoxide and oxalate in DMF should yield the alkylated indoles. Since indole is methylated in ten minutes under these reaction conditions, the acylated indoles ought to react in even less time. The reaction was monitored by TLC for a few hours in both cases. It was noted that if the amount of *t*–butoxide exceeded the amount of oxalate in the mixture, or if undissolved *t*–butoxide was present, the reaction yielded alkylated indoles, but if a slight excess of oxalate was present, no alkylation product was formed. Addition of dissolved indole to this unreactive mixture yielded *N*–alkyl indole almost immediately. Thus we infer that indoles are alkylated under conditions that will not affect the acylated substrates, which consequently are not intermediates in the alkylation reaction. The fact that excess *t*–butoxide could break down **1** and **2** to *N*–alkyl indoles is attributed to liberation of free indole anion by the base. The inhibition of this liberation by excess oxalate can be explained if *t*–butoxide and oxalate forms a much less nucleophilic complex in solution. Such complexes have been isolated by Adickes.[13] To further demonstrate this liberation of indole anion, ethyl 1-oxo-1-(*N*–indolyl)-acetate (**2**) was mixed with a three-fold excess of dimethyl oxalate and a four-fold excess of potassium *t*–butoxide in DMF. This mixture was refluxed overnight and then analyzed by GC. Less than 1% of the alkylated indole was *N*–ethylindole. As expected, *N*–methylindole dominated (>99%).

As a final study of the mechanism, di-*sec*-butyl oxalate and *sec*-butyl tosylate were prepared from the same optically active (S)-*sec*-butanol. Both compounds were used to alkylate *p*–thiocresol using similar conditions. The products were essentially identical, although not enantiomerically pure. Since tosylates are expected to alkylate mainly with inversion, the oxalates obviously alkylate in the same way.

It is notable that the substrate anions can be expected to undergo reversible addition to the acyl carbon of the oxalate in the presence of alkoxides. The alkylations may be dependent on this reversibility to minimize byproducts.

Table I

Literature yields are only from alkylation reactions. In several cases there are better non-alkylative methods available for synthesizing these compounds.

Substrate	Oxalate	Base	Position of Alkylation	Yield (%)	Lit. Yield (%)	Ref
Phenol	Me	Na_2CO_3	O	79	—	—
Phenol	Et	Na_2CO_3	O	67	—	—
Phenol	*sec*-Bu	K_2CO_3	O	25	6	14
p-Thiocresol	Me	*t*-BuOK	S	76	81	15
p-Thiocresol	Et	Na_2CO_3	S	66	91	15
p-Thiocresol	*sec*-Bu	Na_2CO_3	S	67	48	16
o-Mercaptoaniline	Me	K_2CO_3	S	64	54	17
4-Nitroimidazole	Me	*t*-BuOK	1	59	—	9b
Anthranilonitrile	Me	*t*-BuOK	N	85	53	11
2-Aminobenzophenone	Me	*t*-BuOK	N	60	70	24
Indole	Me	*t*-BuOK	N	88	95	18a
Indole	Bn	*t*-BuOK	N	86	95	18a
4-Nitroindole	Me	EtOK	N	91	—	—
4-Nitroindole	Et	EtOK	N	94	—	—
4-Nitroindole	*sec*-Bu	K_2CO_3	N	5	—	—
7-Ethyl-3-methyl-6-nitroindole	Me	EtOK	N	98	—	—
Isatin	Me	K_2CO_3	N	61	80	19a
5-Nitrobenzimidazole	Me	*t*-BuOK	1/3	43/40[a]	71/42[b]	20
Benzotriazole	Me	*t*-BuOK	1/2	59/35[a]	69/38[b]	10a/23
Purine	Me	*t*-BuOK	9	37	30	23
Adenine	Me	*t*-BuOK	9	43	95	21a
Carbazole	Me	*t*-BuOK	N	95	78	22
Carbazole	Et	*t*-BuOK	N	97	85	22
Carbazole	Bn	*t*-BuOK	N	86	97	22

[a] Isolated yields from the same reaction mixture.

[b] Yields from different reactions.

Experimental

^1H NMR-spectra were obtained with a Varian EM 360 (60 MHz), a Bruker WP 200 (200 MHz) or a Bruker AM 400 (400 MHz) using tetramethylsilane as internal standard. The AM 400 was also used for ^{13}C NMR-spectra. Melting points were measured with a Kofler Heizbank-apparatus and are uncorrected.

Dibenzyl oxalate.

Benzyl alcohol (21.6 g, 200 mmol) in toluene (200 mL) was mixed with oxalyl chloride (12.7 g, 100 mmol) and refluxed for a few minutes. The dibenzyl oxalate crystallised from the solution and was collected. Yield 57%, mp 80°C (lit. mp 80°C).[3] ^1H NMR (200 MHz, $CDCl_3$) δ 5.3(4H, s) 7.2-7.5(10H, m). IR (KBr) ν_{max} 3020, 1760, 1490, 1450, 1380, 1240, 1210, 929, 900, 860, 760, 740, 700 cm^{-1}.

Di-*sec*-butyl oxalate.

Oxalyl chloride (63.5 g, 0.5 mol) was added dropwise to *sec*-butanol (111 g, 1.5 mol). The product was distilled at 7 mm Hg, bp 90°C. Yield 142 g (70%). ^1H NMR (200 MHz, $CDCl_3$) δ 0.91(3H, t, J=7.4Hz) 1.3(3H, d, J=6.2Hz) 1.5-1.8(2H, m) 4.97(1H, m, J=6.3Hz). IR (KBr) ν_{max} 2970, 2930, 2880, 1760, 1740, 1455, 1380, 1310, 1210, 1175, 1125, 1105, 1090, 1025, 995, 965, 930, 875, 850 cm^{-1}.

(S,S)-Di-*sec*-butyl oxalate.

Oxalyl chloride (0.79 g, 6.22 mmol) in dry ether (5 ml) was added to (S)-*sec*-butanol (0.92 g, 12.4 mmol) in dry ether (5 ml). The ether was distilled of and the residue distilled in a Kugelrohr apparatus at 0.15 mm Hg. Yield 1.118 g (89%). $[\alpha_D]$= +35.15° (in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.95(3H, t, J=7.5Hz) 1.33(3H, d, J=6.3Hz) 1.6-1.8(2H, m) 4.99(1H, sext, J=6.3Hz). ^{13}C NMR ($CDCl_3$) δ 157.90 (s), 75.43 (d), 28.33 (t), 18.89 (q), 9.30 (q).

(S)-*sec*-Butyl tosylate.

(S)-*sec*-Butanol (1.256 g, 17 mmol) was dissolved in dry pyridine (20 ml) and cooled to 0°C, whereupon *p*-toluenesulfonyl chloride (4.8 g, 25 mmol) was added. The mixture was kept in the freezer for 2 days and then poured onto ice. The water phase was decanted off and the slightly red oil partitioned between 1M HCl and ether. The ether phase was washed with water, dried ($MgSO_4$) and evaporated to give the product as a slightly yellow oil. Yield 1.98 g (51%). $[\alpha_D]$= +9.83° (in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.82(3H, t, J=7.4Hz) 1.24(3H, d, J=6.3Hz) 1.5-1.7(2H, m) 2.44(3H, s) 4.56(1H, sext, J≈6.3Hz) 7.33(2H, d, J=8.5Hz) 7.79(2H, d, J=8.5Hz). ^{13}C NMR ($CDCl_3$) δ 144.41 (s), 134.61 (s), 129.71 (d), 127.68 (d), 81.80 (d), 29.47 (t), 21.61 (q), 20.29 (q), 9.29 (q).

Anisole.

Phenol (0.94 g, 10 mmol) was boiled with sodium carbonate (4 g) in DMF (30 mL) for 10 min. After cooling, dimethyl oxalate (2.36 g, 20 mmol) was added, and the mixture was refluxed for 30 min. The solution was then poured into aqueous ammonia and extracted with ether. The ether solution was washed with water, dried ($MgSO_4$) and evaporated. Yield 0.85g (79%). Bp 150–1°C. ^1H NMR (60 MHz, CCl_4) δ 3.6(3H, s) 6.5-7.2(5H, m).

Ethyl phenyl ether.

Phenol (0.94 g, 10 mmol), diethyl oxalate (2.92 g, 20 mmol) and potassium carbonate (4 g) were refluxed in DMF (30 mL) for 1 h. The reaction mixture was poured into aqueous ammonia and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The product (0.82 g, 67%) distilled at 62°C/8 mm Hg. ^1H NMR (60 MHz, CCl_4) δ 1.3(3H, t, J≈7Hz) 3.85(2H, q, J≈7Hz) 6.5-7.2(5H, m).

sec-Butyl phenyl ether.

Phenol (4.7 g, 50 mmol), *sec*-butyl oxalate (14.14 g, 70 mmol), potassium carbonate (13 g) and pyridine (1 mL) were refluxed in DMF (30 mL) under N_2 for 17 h. Water (30 mL) was added and the solution was refluxed for 10 min. The solution was then extracted with light petroleum. The extract was washed with aqueous NaOH and then evaporated. The residue was distilled at 10 mm Hg, bp 76-7°C (lit. bp_{763} 195-196°C),[14] yield 1.87 g (25%). ^1H NMR (60 MHz, CCl_4) δ 0.95(3H, t, J≈7Hz) 1.2(3H, d, J≈6Hz) 1.3-1.8(2H, m) 4.1(1H, sext, J≈6Hz) 6.6-7.2(5H, m). IR (KBr) ν_{max} 3020, 2960, 2930, 2880, 1600, 1590, 1490, 1375, 1290, 1240, 1125, 1100, 1030, 1000, 920, 880, 790, 750, 690 cm^{-1}.

Methyl *p*-tolyl sulfide.

p-Thiocresol (1.24 g, 10 mmol) and potassium t–butoxide (1.68 g, 15 mmol) were heated at reflux in DMF (30 mL) for 10 min. The solution was cooled, dimethyl oxalate (1.77 g, 15 mmol) was added and the mixture was refluxed for 30 min., whereupon it was poured into aqueous ammonia and then extracted with ether. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was distilled at 8 mm Hg, bp 95°C (lit. bp_{20} 104-105°C),[15] yield 1.05 g (76%). ^1H NMR (60 MHz, CCl_4) δ 2.27(3H, s) 2.38(3H, s) 7.0(4H, s). IR (KBr) ν_{max} 3020, 2990, 2915, 2860, 1495, 1435, 1090, 965, 800 cm^{-1}.

Ethyl *p*-tolyl sulfide.

p-Thiocresol (1.24 g, 10 mmol) was boiled with sodium carbonate (4 g) in DMF (30 mL) under nitrogen for 10 min. The solution was cooled, diethyl oxalate (2.92 g, 20 mmol) was added, and then the solution was refluxed for 30 min. After treatment with aqueous ammonia, the mixture was extracted with ether and the extract washed with water. The ether phase was dried ($MgSO_4$) and evaporated. The residue was distilled at 10 mm Hg, bp 100-1°C (lit. bp_{20} 122-125°C),[15] yield 1.0 g (66%). ^1H NMR (60 MHz, CCl_4) δ 1.24(3H, t, J=7.5Hz) 2.27(3H, s) 2.79(2H, q, J=7.5Hz) 6.8-7.3(4H, m). IR (KBr) ν_{max} 2960, 2290, 1490, 1445, 1395, 1375, 1260, 1200, 1185, 1095, 1020, 965, 800, 760 cm^{-1}.

sec-Butyl *p*-tolyl sulfide.

p-Thiocresol (1.24 g, 10 mmol) and sodium carbonate (4 g) were boiled in DMF (30 mL) for 10 min. After cooling and addition of di-*sec*-butyl oxalate (4.04 g, 20 mmol), the solution was refluxed for 30 min. It was then cooled and treated with aqueous ammonia and extracted with ether. The extract was washed with water, dried ($MgSO_4$), evaporated and distilled at 8 mm Hg, bp 109°C (lit. $bp_{0.3}$ 81-83°C),[16] Yield 1.20 g (67%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.98(3H, t, J=7.4Hz) 1.23(3H, d, J=6.7Hz) 1.4-1.5(1H, m) 1.55-1.7(1H, m) 2.31(3H, s) 3.06(1H, sext, J=6.6Hz) 7.08(2H, ≈d, J≈8Hz) 7.29(2H, ≈d, J≈8Hz). IR (KBr) ν_{max} 2960-2920, 1490, 1470, 1450, 1380, 1205, 1025, 810 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 136.83, 132.77, 131.55, 129.53, 45.36, 29.45, 21.08, 20.52, 11.50

(R)-*sec*-Butyl *p*-tolyl sulfide.

From oxalate: *p*-Thiocresol (223 mg, 1.80 mmol) and (S,S)-di-*sec*-butyl oxalate.(370 mg, 1.83 mmol) were mixed in dry DMF (6 ml), K_2CO_3 (0.65 g) was added and the mixture was heated to 150°C for 30 min. After cooling to room temperature the mixture was poured onto ice and extracted with ether. The extract was washed with aliquots of 2M NaOH and brine, followed by evaporation of the ether. The residue was distilled on a Kugelrohr apparatus at 0.15 mm Hg, giving a clear liquid yield 126 mg (39 %). $[\alpha_D]$= -20.6° (in $CDCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.99(3H, t, J=7.4 Hz) 1.24(3H, d, J=6.7Hz) 1.44-1.69(2H, m) 2.31(3H, s) 3.07(1H, sext, J=6.6Hz) 7.09(2H, d, J≈8Hz) 7.30(2H, d, J≈8Hz). ^{13}C NMR ($CDCl_3$) δ 136.8 (s) 132.7 (d), 131.5 (s), 129.5 (d), 45.3 (d), 29.4 (t), 21.0 (q), 20.5 (q), 11.4 (q).

From tosylate: *p*-Thiocresol (140 mg, 1.13 mmol) and (S)-*sec*-Butyl tosylate.(263 mg, 1.15 mmol) were mixed in dry DMF (5 ml), K_2CO_3 (0.5 g) was added and the mixture was heated to 150°C for 30 min. After cooling to room temperature the mixture was poured onto ice and extracted with ether. The ether was washed with aliquots of 2M NaOH and brine, followed by evaporation of the ether. The residue was partitionated between water and pentane. The pentane was evaporated to give the product as a slight yellow oil, yield 120 mg (59 %). $[\alpha_D]$= -20.2° (in $CHCl_3$). ^1H NMR, ^{13}C NMR as above.

o-Methylthio-aniline.

o-Mercaptoaniline (1.25 g, 10 mmol), dimethyl oxalate (1.77 g, 15 mmol) and potassium carbonate (4 g) were refluxed in DMF (30 ml) under N_2 for 30 min. The reaction mixture was partitioned between ether and water. The ether phase was then washed with brine, dried ($MgSO_4$) and evaporated. The residue was distilled at 0.05 mm Hg, bp 62-3°C (lit. bp_{36} 141.5-143°C),[17] yield 0.89 g (64%). ^1H NMR (60 MHzCCl_4) δ 2.2(3H, s) 4.1(2H, br. s) 6.3-7.3(4H, m). IR (KBr) ν_{max} 3440, 3340, 3060, 3010, 2990, 2920, 1610, 1480, 1450, 1305, 1250, 1150, 1080, 1020, 970, 750 cm^{-1}.

General procedure for the N-alkylations.

Substrate (30 mmol), dialkyl oxalate (30 mmol) and potassium t-butoxide (3.36 g, 30 mmol) are refluxed in DMF (50 ml) for 3 h. Addition of aqueous ammonia, extraction with methylene chloride and evaporation of the solvent gives the crude product.

1-Methyl-4-nitroimidazole.

The product was obtained by recrystallisation from methanol. Yield 59%, mp 134°C (lit. mp 133°C).[9b] ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.87(3H, s) 7.41(1H, br. s) 7.78(1H, d, J=1.5Hz).

N-Methyl-2-aminobenzophenone.

A mixture of 2-aminobenzophenone (3.94 g, 20 mmol), dimethyl oxalate (3.39 g, 30 mmol), and potassium t-butoxide (3.36 g, 30 mmol) in DMF (45 ml) was refluxed for 2 h. After evaporation the residue was partitioned between water and CH_2Cl_2. The organic phase was dried and purified (washing through a short silica column) to give yellow crystals, 2.34 g (60%), mp 70–1°C (lit. mp 69°C).[24] IR (KBr) ν_{max} 3349, 1623, 1566, 1518, 1419, 1262, 1173, 1139, 919, 756, 744, 701, 644 cm^{-1}.

1-Methylindole.

The reaction time was 10 minutes. The product was obtained by distillation of the crude product. Yield 88%, bp_{20} 119-25°C (lit. bp_8 95°C).[18b] ^{1}H NMR (60 MHz, CCl_4) δ 3.3(3H, s) 6.3-7.7(6H, m).

1-Benzylindole.

The product was obtained by distillation of the crude product and two subsequent recrystallisations, from light petroleum and ethanol respectively. Yield 86%, mp 40-42°C (lit. mp 45°C).[18a] IR (KBr) ν_{max} 3100, 2980, 1500, 1480, 1340, 1200, 1090, 1020, 760, 730, 640 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.3(2H, s) 6.5(1H, d, J=3.1Hz) 7.0-7.4(9H, m) 7.65(1H, d, J≈6.7Hz). MS *m/z* 207(M$^+$), 92, 91(100), 65.

1-Methyl-4-nitroindole.

The product was obtained by recrystallisation from methanol. Yield 91%, mp 112-6°C. IR (KBr) ν_{max} 3500-3300, 3100, 1620, 1560, 1500, 1470, 1360, 1330, 1310, 1290, 1080, 950, 790, 750, 730 cm^{-1}. ^{1}H NMR(60 MHz, $CDCl_3$) δ 3.8(3H, s) 7.0-7.3(3H, m) 7.6(1H, d, J=7.5Hz) 8.1(1H, dd, J_1=8Hz, J_2=1Hz).

1-Ethyl-4-nitroindole.

The product was obtained by recrystallisation from methanol. Yield 94%, mp 50.5°C. ^{1}H NMR(400 MHz, $CDCl_3$) δ 1.51(3H, t, J=7.3Hz) 4.26(2H, q, J=7.3Hz) 7.2-7.3(2H, m) 7.39(1H, d, J=3.1Hz) 7.67(1H, d, J=8.1Hz) 8.14(1H, dd, J_1=8.0Hz, J_2=0.8Hz).

1,3-Dimethyl-7-ethyl-6-nitroindole.

N–methylation. The product was obtained by recrystallisation from methanol. Yield 98%, mp 114-8°C. ^{1}H NMR(60 MHz, $CDCl_3$) δ 1.42(3H, t, J=7.5Hz) 2.27(3H, s) 3.16(2H, q) 4.03(3H, s) 6.87(1H, br. s) 7.29(1H, d, J=9Hz) 7.52(1H, d).

1-Methyl-5-nitrobenzimidazole and 1-Methyl-6-nitrobenzimidazole.

The products were obtained by fractional crystallisation of the evaporated extract. Yields (from ^{1}H NMR of crude product). 1-Methyl-5-nitrobenzimidazole: 43% yield mp 209-11°C (lit. mp 212°C).[20] ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.94(3H, s) 7.40(1H, d, J=8.5Hz) 8.02(1H, br. s) 8.20(1H, dd) 8.67(1H, d, J=2Hz). 1-Methyl-6-nitrobenzimidazole: 40% yield mp 181-2 °C (lit. mp 182°C).[20] ^{1}H NMR (60 MHz, $CDCl_3$): 3.97(3H, s) 7.79(1H, d, J=9Hz) 8.09(1H, br. s) 8.09-8.35(2H, m).

1-Methyl-1H-benzotriazole and 2-Methyl-2H-benzotriazole.

The crude product was an isomeric mixture from which 1-methyl-1H-benzotriazole was removed by extraction with hydrochloric acid (5M) giving 2-methyl-2H-benzotriazole as a yellow oil, Yield 1.38 g (35%), bp_{10} 104-5°C (lit. bp_{17} 106-7°C).[23] ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.3(3H, s) 7.0-7.3(2H, m) 7.7-7.9(2H, m). The acid extract was made alkaline and extracted with ether giving 1-methyl-1H-benzotriazole as white plates, yield 2.36 g (59%), mp 64-5°C (lit. mp 65°C).[10a] ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.2(3H, s) 7.1-7.4(3H, m) 7.8-8.0(1H, m).

N–Methylisatin.

Isatin (1.47 g, 10 mmol), dimethyl oxalate (1.77 g, 15 mmol) and potassium carbonate (4 g) were refluxed in a 50/50 mixture of DMF and THF (30 ml) for 3 h. Dimethyl oxalate (0.59 g, 5 mmol) was added and the solution was refluxed for 2 more hours. Acetic acid (10 ml) was added and the mixture was extracted with dichloromethane. The extract was evaporated, charcoal was added and the residue was sublimed under vacuum at 0.02 mm Hg, temp. 100°C. The yield was 0.99 g (61%), mp 126-8°C (lit. mp 136°C).[19b] ^{1}H NMR(60 MHz, $CDCl_3$) δ 3.2(3H, s) 6.7-7.7(4H, m). IR (KBr) v_{max} 3420, 3050, 1715, 1605, 1465, 1420, 1365, 1325, 1250, 1155, 1110, 1090, 1030, 955, 860, 815, 770, 755 cm^{-1}.

9-Methyl-9H-purine.

Purine (2.40 g, 20 mmol), dimethyl oxalate (2.36 g, 20 mmol) and potassium t–butoxide (2.24 g, 20 mmol) were refluxed in DMF (60 ml) for 1 h, whereafter the solvent was evaporated. The residue was chromatographed on silica using a CH_2Cl_2-MeOH gradient giving the product as white crystals. Yield 37%, mp 163-5°C (lit. mp 160-2°C).[23] ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ 3.84(3H, s) 8.55(1H, s) 8.93(1H, s) 9.13(1H, s). ^{13}C NMR ($DMSO_{d6}$) δ 151.9 (d), 147.6 (d), 147.6 (d), 29.4 (q).

9-Methyl-9H-adenine.

The procedure used for alkylating purine was also used for adenine. The residue after evaporation was extracted with acetonitrile (≈300 ml) and the extract was treated with charcoal and filtered. From this solution, 9-methyl-9H-adenine deposited upon cooling. Yield 1.28 g (43%), mp 297-9°C (lit. mp 310°C).[21b] ^{1}H NMR (400 MHz, DMSO$_{d6}$) δ 3.70(3H, s) 7.18(2H, br. s) 8.07(1H, s) 8.13(1H, s). ^{13}C NMR (DMSO$_{d6}$) δ 155.9 (s), 152.4 (d), 141.3 (d), 29.3 (q).

9-Methylcarbazole.

Carbazole (33.4 g, 0.2 mol), dimethyl oxalate (28.3 g, 0.24 mol) and potassium t–butoxide (26.8 g, 0.24 mol) were refluxed in DMF (400 ml) for 1h. The cooled reaction mixture was poured into ammonia (aq, 5%, 1.5 l). The precipitated product was collected after 1 h, washed with water, dried and recrystallised from ethanol/H_2O. Yield 34.4 g (95%), mp 87-8°C (lit. 87-8°C).[22]

9-Ethylcarbazole.

The procedure given for 9-methylcarbazole was also used for 9-ethylcarbazole. Yield 97%, mp 64-5°C (lit. 65-6°C).[22]

9-Benzylcarbazole.

Carbazole (1.67 g, 10 mmol), dibenzyl oxalate (3.24 g, 12 mmol) and potassium t–butoxide (1.34 g, 12 mmol) were refluxed for 30 min. in DMF (40 ml). The product was precipitated from ice, filtered off and washed with methanol. Yield 2.22 g (86%). Mp 121°C (lit. 119-20°C).[22] IR (KBr) ν_{max} 3080, 1640, 1610, 1500, 1470, 1350, 1220, 1160, 760, 730 cm^{-1}. ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.4(2H, s) 7.0-7.5(11H, m) 7.9-8.2(2H, m). MS *m/z* 257(M$^+$), 207, 92, 91(100), 65.

Ethyl α-oxo-α-(N–indolinyl)-acetate

Indoline (6.85 g, 58 mmol) was carefully added dropwise to oxalic acid monoethyl ester monochloride (9 ml, 54 mmol). A yellowish salt formed violently. THF (20 ml) was added and the mixture was refluxed for 2h. The solvent was evaporated and the oily residue was poured into ice. The solid formed was dissolved in methanol and poured onto ice/water to give a crude product which was recrystallized from cyclohexane to give white crystals, yield 7.92 g (63%), mp 36.5-39°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4(3H, t, J=7.1Hz) 3.2(2H, t, J=8.3Hz) 4.25(2H, t, J=8.5Hz) 4.4(2H, q, J=7.0Hz) 7.05-7.3(3H, m) 8.2(1H, m).

Methyl α-oxo-α-(N–indolinyl)-acetate

Indoline (8.3 g, 70 mmol) was dissolved in THF (30 mL) was added to a solution of oxalic acid monomethyl ester monochloride (9.7 g, 80 mmol) in THF (20 ml) at -78°C. A precipitate formed on addition. The mixture was refluxed for 20 min, whereupon the now clear solution was evaporated. The residue was dissolved in ethanol and poured onto ice to give a solid crude product which was further crystallized from light petroleum at -78°C to give white crystals, yield 11.53 g (80%), mp 38-41°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.2(2H, t, J=8.3Hz) 3.9(3H, s) 4.25(2H, t, J=8.4Hz) 7.0-7.3(3H, m) 8.2(1H, m). IR(film) ν_{max} 2960, 1740, 1660, 1600, 1490, 1470, 1440, 1420, 1260, 1210, 1100, 760 cm^{-1}.

Methyl α-oxo-α-(N–indolyl)-acetate (1)

Methyl α-oxo-α-(N–indolinyl)-acetate (2.05 g, 10 mmol) and DDQ (2.4 g, 10.5 mmol) were refluxed in dioxane for 5 h. The solution was filtered and evaporated. The residue was subjected to flash chromatography on silica with light petroleum. The resulting oil was distilled in a kugelrohr apparatus at 0.8 mm Hg with an oven temperature of 250°C. The product solidified into a white mass, mp 38-43°C. Yield 0.66 g (33%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.0(3H, s) 6.7(1H, d, J=3.5Hz) 7.25-7.45(2H, m) 7.5-7.65(2H, m) 8.4(1H, br. d, J=6Hz). IR(film) ν_{max} 3180, 2960, 1745, 1710, 1455, 1440, 1270, 1215, 1080, 990, 795, 780, 770, 760, 735 cm^{-1}. MS *m/z* 204, 203(M$^+$,100) 175, 149, 144, 131, 130, 117, 116, 90, 89.

Ethyl α-oxo-α-(N–indolyl)-acetate (2)

Ethyl α-oxo-α-(N–indolinyl)-acetate (4.38 g, 20 mmol) and DDQ (5 g, 22 mmol) were refluxed in dioxane (40 mL) overnight. The solution was filtered and the filtrate evaporated. The residue was subjected to flash chromatography on silica with methylene chloride. After evaporation the product was distilled to give an oil, bp$_{0.09}$ 113°C, yield 1.6 g (37%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4(3H, t, J=7.1Hz) 4.4(2H, q, J=7.1Hz) 6.6(1H, d, J=3.9Hz) 7.2-7.35(2H, m) 7.45-7.55(2H, m) 8.4(1H, br. d, J=7.4Hz). IR(film) ν_{max} 2980, 1740, 1700, 1450, 1400, 1350, 1260, 1190, 1100, 1080, 1010, 770, 750 cm^{-1}. MS *m/z* 218, 217(M$^+$,100), 144, 130, 117, 116, 90, 89.

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