Remarkable Selectivity in the Reaction of 1-Trityl-2-lithioimidazoles with *t*-Butyl Halogenoacetates

Ian G. C. Coutts*, Shende Jieng, Ghanshyam D. Khandelwahl, and Michael L. Wood

Department of Chemistry and Physics, Nottingham Trent University, Clifton Lane, Nottingham NG11 8NS, England

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2-Lithio-1-triphenylmethylimidazoles react with *t*-butyl halogenoacetates to give a variety of products, the nature of which is cleanly determined by the halogen atom. With chloroacetate the products are chloromethyl ketones, while bromacetate gives di-*t*-butyl imidazolesuccinates, and iodoacetate yields iodoimidazoles. In each case 50% of the parent triphenylmethylimidazole is recovered from the reaction. When the triphenylmethyl substituent is replaced by the *N,N*-dimethylsulfamoyl group, reaction with bromoacetate is suppressed, but *t*-butyl chloroacetate and iodoacetate again give chloroketones and aryl iodides respectively.

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In the course of an investigation involving simple analogues of the antifungal drug ketoconazole we required a versatile means of synthesizing a range of 1-tritylimidazoles **1**. Although these can be obtained by tritylation of the corresponding imidazoles, polyfunctional members of the latter class of compounds are often difficult to prepare, and regiospecific *N*-alkylation to give the desired product cannot be guaranteed.

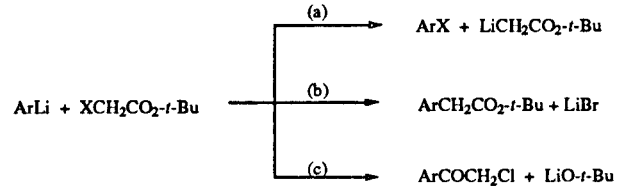
A useful strategy [1] for obtaining substituted *N*-alkylimidazoles is nuclear lithiation followed by quenching with electrophiles, and 2-lithio-1-trityl imidazole, **2a**, has been reacted with *n*-propyl nitrate [2] and diphenyl disulfide [3] to afford the corresponding 2-nitro- and 2-phenylthioimidazoles, while a high-yielding synthesis [4] of 2-substituted imidazoles uses the reaction of **2a** with halogen sources, iodomethane or DMF, followed by removal of the trityl group. The suitability of trityl as a nitrogen-blocking group during the formation of 2,5-dilithioimidazoles has been discussed [5].

The 2-lithioimidazoles **2a**, **2b**, and **2d** reacted with benzaldehyde, benzophenone, dimethyl disulfide, and iodomethane to give the expected products, but, in accord with previous findings [6], no imidazole-2-carboxylic acids were obtained by quenching with carbon dioxide. More surprising was our failure, in repeated experiments, to isolate any aldehydes from the reaction of the lithium reagents with DMF. In an attempt to introduce into our tritylimidazoles a carbonyl function (albeit in a side chain) attention was next directed to the reaction of **2** with halogenoacetates, with unusual results.

In theory an organolithium reagent ArLi and an ester XCH_2CO_2R can react (Scheme) a) by halogen-metal exchange to give an aryl halide, b) by an S_N process at the CH_2 yielding an arylacetate, and c) by nucleophilic attack on the carbonyl carbon, leading to a halomethyl ketone. The aryl anion may also abstract a proton from a methylene group adjacent to the carbonyl of the initial ester or of a reaction product.

It appears that the products of the reaction of lithioimidazoles **2** with *t*-butyl halogenoacetates may arise from any of the pathways of the Scheme, *but that the nature of the product obtained is cleanly determined by the nature of the halogen atom.* The results are summarized in the Table.

Scheme



Table

Products of the Reaction of Lithioimidazoles **2**, **7** with XCH_2CO_2-*t*-Bu

2-Lithioimidazole	X = Cl	X = Br	X = I
2a	**5a** (54)[a]	**3a** (88)	**4a** (62)
2b	0	**3b** (63)	**4b** (59)
2c	0	**3c** (91)	**4c** (80)
2d	**5d** (91)	**3d** (63)	**4d** (74)
2e	0	**3e** (61)	0
7a	**8d** (66)	0	**9a** (26)
7b	**8b** (67)	0	0

(a) Yield (%) of purified product, calculated on the 50% of **1**, **6** which was converted during the reaction.

When organolithiums **2a** to **2e** were reacted at -10° in THF with *t*-butyl bromoacetate, followed by hydrolysis, the di-*t*-butyl imidazolesuccinates **3a** to **3e** were obtained as the sole products. It is likely that succinates **3** arise by preliminary formation of acetates, (Scheme, path b). Proton abstraction from these esters and subsequent reaction of the resulting carbanion with further bromoacetate gives the imidazolesuccinate.

$$2 + t\text{-}BuO_2CCH_2Br \rightarrow t\text{-}BuO_2CCH_2Ar + LiBr$$
$$t\text{-}BuO_2\ CCH_2Ar + 2 \rightarrow t\text{-}BuO_2CCH(Li)Ar + 1$$
$$t\text{-}BuO_2CCH(Li)Ar + t\text{-}BuO_2CCH_2Br \rightarrow 3$$

This is supported by recovery of 50% of **1** from each reaction, and by the efficient (82% yield) preparation of di-*t*-butyl phenylsuccinate from sequential treatment at low temperature of *t*-butyl phenylacetate with phenyllithium and *t*-butyl bromoacetate.

Unfortunately the transformation of **2** to **3** is highly specific, and does not constitute a general route to arylsuccinates. Reaction of **2b** with ethyl or benzyl bromoacetates gave mixture of products, as did treatment of *t*-butyl bromoacetate with phenyllithium or with 2-lithio-1-tritylbenzimidazole.

When 2-lithioimidazoles **2a** to **2d** were reacted at -10° with *t*-butyl iodoacetate, there were isolated from the reaction mixture the corresponding imidazole **1**, (50%), di-*t*-butyl succinate, and the 2-iodoimidazoles **4a** to **4d**, products of halogen-metal exchange, [Scheme, route (a)]. No arylsuccinates were formed. From the reaction of **2c** with two molar equivalents of *t*-butyl iodoacetate no starting imidazole **1c** was detected in the final product, and iodoimidazole **4c** was obtained in 78% yield. These findings are consistent with the reaction sequence.

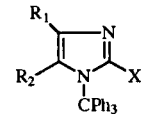
$$2 + t\text{-}BuO_2CCH_2I \rightarrow 4 + t\text{-}BuO_2CCH_2Li$$
$$t\text{-}BuO_2CCH_2Li + t\text{-}BuO_2CCH_2I \rightarrow (t\text{-}BuOC_2CH_2\text{-})_2$$

The most striking results were obtained when **2a** and **2d** were treated with *t*-butyl chloroacetate. Again 50% of **1a** or **1d** was recovered, but the sole products, consistently formed in duplicate experiments were the chloroketones **5a**, **5d**, formed by an unusual nucleophilic displacement of the *t*-butoxide anion from the ester by the bulky species **2**. No chloroketones were obtained from **2b**, **2c** or **2e**.

The selectivity of the above reaction is dependent on both the organolithium species and the electrophile. Replacement of the trityl group of **2** by *N,N*-dimethylsulfamoyl gave lithioimidazoles **7** in which the sulfonamide substituent stabilises [5] the 2-anion. Compounds **7a**, **7b** gave reasonable yields of chloroketones **8a**, **8b**, but did not react with *t*-butyl bromoacetate, and only **7a** reacted with iodoacetate to afford iodoimidazole **9a** in low yield.

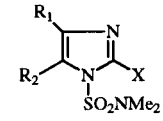
Conclusion.

This investigation provides an unusually clear-cut example of the products obtainable fom the reaction of organolithiums with halogenoacetates, and illustrates the caution needed in studies on the lithiation of imidazoles based on quenching intermediate anions with apparently equivalent electrophiles.



1 X = H
2 X = Li
3 X = CH(CO_2-*t*-Bu)CH_2CO_2-*t*-Bu
4 X = I
5 X = $COCH_2Cl$

a) $R_1 = R_2 = H$
b) R_1 = Me, R_2 = H
c) $R_1 R_2$ = Me
d) R_1 = Ph, R_2 = H
e) $R_1 = R_2$ = Ph



6 X = H
7 X = Li
8 X = $COCH_2Cl$
9 X = I

a) R_1 = Ph, R_2 = H
b) R_1 = Ph, R_2 = Me

EXPERIMENTAL

The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform solution on a JEOL EX 270 spectrometer, with TMS as the internal standard. Elemental analyses and mass spectra (chemical ionization) were determined by Shell Research, Sittingbourne, England. Tetrahydrofuran was distilled from calcium hydride or sodium benzophenone ketyl; other solvents were dried over 5Å molecular sieves. Petroleum ether had bp 60-80°. Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) with redistilled eluting solvents.

t-Butyl iodoacetate, bp 100°/20 mm was prepared by the reaction in refluxing acetone of sodium iodide with *t*-butyl chloroacetate. Imidazole, 4-methyl- and 4,5-diphenylimidazole were purchased fom Aldrich; 4-phenyl -[7], 4,5-dimethyl- [7] and 4-methyl-5-phenylimidazoles [8] were prepared according to literature methods. Reactions of the imidazoles with chlorotriphenylmethane in dichloromethane containing triethylamine [2] gave the known 1-triphenylmethyl derivatives of imidazole (**1a**) [9], 4,5-dimethylimidazole (**1c**) [9], 4,5-diphenylimidazole (**1e**) and 4-methylimidazole (**1b**) [2].

4-Phenyl-1-triphenylmethylimidazole (**1d**).

This compound was prepared similarly and was recrystallized from ethyl acetate, mp 190-191°; ms: m/z 385.

Anal. Calcd. for $C_{28}H_{22}N_2$: C, 87.0; H, 5.7; N, 7.2. Found: C, 86.9; H, 5.9; N, 7.2.

N,N-Dimethyl-4-phenylimidazole-1-sulfonamide (**6a**).

To a stirred solution of 4-phenylimidazole (5 g) and dimethylsulfamoyl chloride (5 g) in dry dichloromethane (50 ml) was added triethylamine (5 ml) in dichloromethane (25 ml). Stirring was continued for 72 hours, with a further addition of sulfamoyl chloride (5 g) and triethylamine (5 ml) after 36 hours. The mixture was poured into water (250 ml), the separated organic layer washed with brine, dried over magnesium sulfate, evaporated and the residue purified by flash chromatography (chloroform as eluant) and crystallization from ethyl acetate-petroleum ether to afford the sulfonamide **6a**, 61%, mp 104-105°; ^1H nmr: δ 2.92 (s, 6H); ^{13}C nmr: δ 38.2.

Anal. Calcd. for $C_{11}H_{13}N_3O_2S$: C, 52.6; H, 5.2; N, 16.7. Found: C, 52.4; H, 5.1; N, 16.8.

N,N-Dimethyl-5-methyl-4-phenylimidazole-1-sulfonamide (**6b**).

This compound was prepared similarly from 4-methyl-5-phenylimidazole and crystallized from ethyl acetate-petroleum ether, 67% yield, mp 102-103°; ^{1}H nmr: δ 2.55 (s, 3H), 2.92 (s, 6H) 7.31-7.66 (m, 5H), 7.95 (s, 1H); ^{13}C nmr: δ 10.8, 38.0; ms: m/z 265.

Anal. Calcd. for $C_{12}H_{15}N_3O_2S$: C, 54.3; H, 5.6; N, 15.8. Found: C, 54.5; N, 5.7; N, 16.2.

General Procedure for the Reaction of 2-Lithioimidazoles with *t*-Butyl Halogenoacetates.

To a solution of the protected imidazole **1** or **6** (10 mmoles) in dry tetrahydrofuran (150 ml) was added with stirring under nitrogen at -60° a solution of *n*-butyllithium in hexanes (1.6 *M*, 7 ml). The mixture was allowed to warm to -10° over 1 hour, and a solution of the acetate (10 mmoles) in tetrahydrofuran (5 ml) was added in one portion. The reaction was allowed to reach room temperature with stirring over 2-3 hours, and was quenched with ice-water and extracted with ether. The separated organic layer was dried, evaporated, and the residue recrystallized, preceded if necessary by flash chromatography.

Di-*t*-butyl 1-Triphenylmethylimidazole-2-succinate (**3a**).

The crude product obtained from the reaction of 2-lithio-1-triphenylmethylimidazole (**2a**) with *t*-butyl bromoacetate as described above was subjected to flash chromatography with ethyl acetate (1 part) and petroleum ether (6 parts) as the eluant. Succinate **3a** was obtained in the early fractions, followed by 1-triphenylmethylimidazole, and was recrystallized from aqueous ethanol, mp 192-193°; ir: ν CO 1740 cm^{-1}; ^{1}H nmr: δ 1.30 (s, 9H), 1.48 (s, 9H), 2.1-2.65 (m, 2H), 3.8 (dd, 1H); ^{13}C nmr: δ 28.0, 35.45, 43.0, 81.0, 169.5, 170.5; ms: m/z 538.

Anal. Calcd. for $C_{34}H_{38}N_2O_4$: C, 75.8; H, 7.1; N, 5.2. Found: C, 75.8; H, 7.1; N, 5.2.

Di-*t*-butyl 4-Methyl-1-triphenylmethylimidazole-2-succinate (**3b**).

This compound was prepared similarly from **2b** and recrystallized from ethyl acetate-petroleum ether, mp 175-176°; ^{13}C nmr: 13.6, 28.0, 35.5, 42.8, 81.0, 169.5, 170.5; ms: m/z 552.

Anal. Calcd. for $C_{35}H_{40}N_2O_4$: C, 76.1; H, 7.2; N, 5.1. Found: C, 75.7; H, 7.2; N, 5.2.

Di-*t*-butyl 4,5-Dimethyl-1-triphenylmethylimidazole-2-succinate (**3c**).

This compound was prepared fom 4,5-dimethyl-1-triphenylmethylimidazole, and recrystallized from ether-petroleum ether, mp 156-157°; ir: ν CO 1730 cm^{-1}; ^{13}C nmr: δ 13.0, 13.5, 28.0, 37.8, 42.3, 81.1, 170.0, 170.3; ms: m/z 566.

Anal. Calcd. for $C_{36}H_{42}N_2O_4$: C, 76.3; H, 7.4; N, 5.0. Found: C, 75.9; H, 7.4; N, 5.0.

Di-*t*-butyl 4-Phenyl-1-triphenylmethylimidazole-2-succinate (**3d**).

This compound was prepared fom 4-phenyl-1-triphenylmethylimidazole, and recrystallized from ether-petroleum ether, mp 165-166°; ir: ν CO 1738, 1725 cm^{-1}; ^{13}C nmr: δ 28.0, 35.3, 43.3, 81.1, 169.5, 170.7; ms: m/z 614.

Anal. Calcd. for $C_{40}H_{42}N_2O_4$: C, 78.2; H, 6.8, N, 4.6. Found: C, 78.2; H, 6.9; N, 4.6.

Di-*t*-butyl 4,5-Diphenyl-1-triphenylmethylimidazole-2-succinate (**3e**).

This compound was prepared fom 4,5-diphenyl-1-triphenylmethylimidazole, and recrystallized from ethyl acetate-petroleum ether, mp 161-162°; ms: m/z 690.

Anal. Calcd. for $C_{46}H_{46}N_2O_4$: C, 80.0; H, 6.7; N, 4.1. Found: C, 79.7; H, 6.8; N, 4.1.

Di-*t*-butyl Phenylsuccinate.

t-Butyl phenylacetate (3.0 g) was reacted with *n*-butyllithium and then with *t*-butyl bromoacetate (3.1 g) by the general procedure. The oil obtained on standard work-up yielded after short-path distillation, di-*t*-butyl phenylsuccinate (82%), bp 200°/30 mm; ^{1}H nmr: δ 1.38 (s, 9H), 1.40 (s, 9H), 2.5 (1H, dd), 3.0 (1H, dd), 3.9 (1H, dd); ^{13}C nmr: δ 27.8, 39.0, 48.5, 80.9, 170.8, 172.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.6; H, 8.5. Found: C, 70.5; H, 8.5.

The ester was dissolved in trifluoroacetic acid, and after 5 hours the precipitated solid was collected and recrystallized from aqueous ethanol to give phenylsuccinic acid, mp 168-170°, identical with an authentic sample.

2-Iodo-1-triphenylmethyimidazole (**4a**).

The product mixture resulting from the reaction under standard conditions of **2a** (10 mmoles) and *t*-butyl iodoacetate (10 mmoles) was subjected to flash chromatography with ethyl acetate (1 part) and petroleum ether (6 parts). The residue obtained from evaporation of an early fraction, on trituration* with petroleum, yielded a solid which crystallized from ethyl acetate-petroleum ether to give 2-iodo-1-triphenylmethylimidazole (1.36 g), mp 175-176° (lit [4] mp 170-172°); ms: m/z 436.

Anal. Calcd. for $C_{22}H_{17}IN_2$: C, 60.6; H, 3.9; N, 6.4 Found: C, 60.5; H, 3.9; N, 6.5.

Further elution with ethyl acetate gave 1-tritylimidazole (1.36 g, 50%).

*Evaporation of the petroleum ether triturate and bubble distillation of the residue yielded di-*t*-butyl succinate, bp 110°/0.05 mm (0.5 g), the ^{1}H nmr of which agreed with that previously reported [10] for the diester.

2-Iodo-4-methyl-1-triphenylmethylimidazole (**4b**).

This compound was obtained by the above procedure from **2b**, and recrystallized from ethyl acetate-petroleum ether, mp 182-183°; ms: m/z 450.

Anal. Calcd. for $C_{23}H_{19}IN_2$: C, 61.3; H, 4.2; N, 6.2; Found: C, 61.2; H, 4.4; N, 6.3.

4,5-Dimethyl-2-iodo-1-triphenylmethylimidazole (**4c**).

This compound was obtained similarly from **2c**, and recrystallized from ethyl acetate-petroleum ether, mp 136-137°; ms: m/z 464.

Anal. Calcd. for $C_{24}H_{21}IN_2$: C, 62.1; H, 4.5; N, 6.0. Found: C, 62.5; H, 4.8; N, 6.0.

2-Iodo-4-phenyl-1-triphenylmethylimidazole (**4d**).

This compound was obtained from the reaction of **2d** (10 mmoles) and *t*-butyl iodoacetate. The following were isolated: di-*t*-butyl succinate (0.55 g), 4-phenyl-1-triphenylmethylimidazole (1.64 g) and iodo compound **4d** (1.88 g) which was recrystallized from ethanol, mp 167-169°; ms: m/z 512.

Anal. Calcd. for $C_{28}H_{21}IN_2$: C, 65.6; H, 4.1; N, 5.5. Found: C, 66.0; H, 4.4; N, 5.8.

The iodoimidazole was also obtained in low yield by the reaction of **2d** with *N*-iodosuccinimide.

N,N-Dimethyl-2-iodo-4-phenylimidazole-1-sulfonamide (**9a**).

This compound was obtained fom the reaction of **7a** with iodoacetate, and recrystallized from ethyl acetate-petroleum ether, mp 127-128°.

Anal. Calcd. for $C_{11}H_{12}IN_3O_2S$: C, 35.0; H, 3.2; N, 11.1. Found: C, 35.4; H, 3.4; N, 11.2.

2-Chloroacetyl-1-triphenylmethylimidazole (**5a**).

This compound was obtained from the reaction of **2a** with *t*-butyl chloroacetate and purified by flash chromatography with ethyl acetate (1 part) and petroleum ether (6 parts) as the eluant, followed by recrystallization from ethyl acetate-hexane to afford the chloroketone **5a**, mp 182-183°; ir: ν CO 1720 cm^{-1}; ^1H nmr: δ 4.60 (s, 2H); ^{13}C nmr: δ 42.1, 179.3.

Anal. Calcd. for $C_{24}H_{19}ClN_2O$: C, 74.5; H, 4.9; N, 7.2. Found: C, 74.9; H, 5.2; N, 7.2.

2 Chloroacetyl-4-phenyl-1-triphenylmethylimidazole (**5d**).

This compound was prepared by the reaction of **2d** with the chloroacetate, mp 173-174°; ir: ν CO 1732 cm^{-1}; ms: FAB m/z 462; ^1H nmr: δ 4.7 (s, 2H); ^{13}C nmr: δ 47.5, 179.6.

Anal. Calcd. for $C_{30}H_{23}ClN_2O$: C, 77.9; H, 5.0; Cl, 7.6; N, 6.1. Found: C, 77.5; H, 5.1; Cl, 7.4; N, 6.0.

N,N-Dimethyl-2-chloroacetyl-4-phenylimidazole-1-sulfonamide (**8d**).

This compound was obtained from the reaction of **7a** with *t*-butyl chloroacetate, mp 173-174°; ir: ν CO 1720 cm^{-1}; ^1H nmr: δ 3.12 (s, 6H), 5.0 (s, 2H); ^{13}C nmr: δ 38.9, 47.3, 181.2.

Anal. Calcd. for $C_{13}H_{14}ClN_3O_3S$: C, 47.6; H, 4.3; N, 12.8. Found: C, 47.6; H, 4.4; N, 12.6.

N,N-Dimethyl-2-chloroacetyl-5-methyl-4-phenylimidazole-1-sulfonamide (**8b**).

This compound was obtained from the reaction of **7b** with *t*-butyl chloroacetate, mp 106-107°; ir: ν CO 1740 cm^{-1}; ^1H nmr: δ 2.61 (s, 3H), 3.16 (s, 6H), 4.94 (s, 2H); ^{13}C nmr: δ 12.9, 38.7, 48.0, 182.6.

Anal. Calcd. for $C_{14}H_{16}ClN_3O_3S$: C, 49.2; H, 4.7; N, 12.9. Found: C, 48.7; H, 4.9; N, 12.5.

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