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Bis-Trimethylsilylacetamide: A Reagent for the Control of Friedel-Crafts Alkylation Reactions Using Methyl Chloromethoxyacetate

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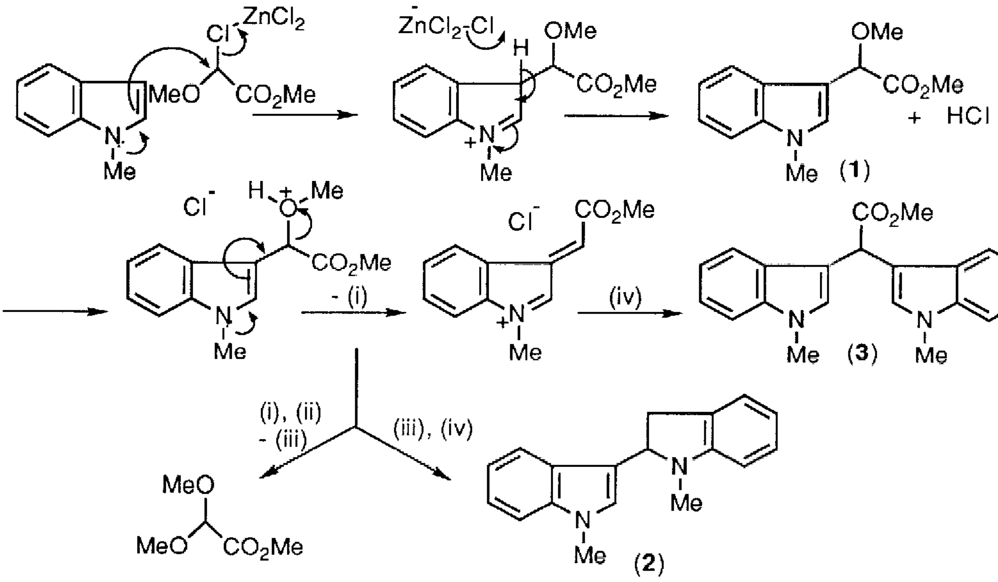
Key words: di-cation equivalent; α-methoxyarylacetic acid; diarylacetic acid; π-excessive heterocycle; hydrogen chloride scavenger;

Abstract: *The Friedel-Crafts alkylation reactions of electron rich aromatic compounds using methyl α-chloro-α-methoxyacetate and Lewis acids leads predominantly to the formation of diarylacetic acid derivatives in which the second stage of the sequence is favoured by the presence of hydrogen chloride generated in the first step; effective control can be achieved in a number of cases by the addition of bis-trimethylsilylacetamide.*

There are a number of examples where Friedel-Crafts alkylation reactions of electron rich aromatic compounds are difficult to control. Water functions as a co-catalyst in Friedel-Crafts reactions by interaction with the Lewis acid and an equivalent of protic acid is also generated during the reaction.[1] This can cause destruction of the substrate, for example the dimerisation or trimerisation of indole and its derivatives.[2] In the case of compounds that can function as polyfunctional reagents, for example aldehydes and ketones, it may be difficult to stop reactions at a given stage as exemplified by the acid catalysed reaction of thiophene with acetone.[3] There are many other examples where reactions give products in which more than one equivalent of the aromatic substrate has reacted.[4] Our interest in reactions of polyfunctional alkylating agents[5] and the importance of devising new synthetic approaches to α-heteroatom substituted carboxylic acids, for example α-amino acids,[6] and α-alkoxyacetic acid derivatives,[7] prompted our investigation of Friedel-Crafts reactions of esters of α-halo-α-methoxyacetic acid some of which are reported herein. Reactions of methyl chloromethoxyacetate with, for example benzene and toluene, have been reported previously[8] but there are no reports of studies using π-excessive heterocyclic or carbocylic substrates.

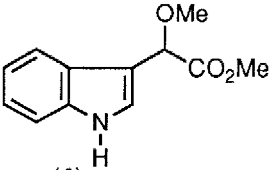
Problems associated with reactions of π-excessive aromatic compounds are exemplified by our results using *N*-methylindole. A reaction of *N*-methylindole (15 mmol) with methyl chloromethoxyacetate (5 mmol) and zinc chloride (4.9 mmol) in THF at room temperature (for 2h) gave the di-indolylacetate derivative (**3**)[9] in 68% yield and the *N*-methylindole dimer (**2**)[10] in 32% yield together with methyl dimethoxy-acetate (19%) and recovered *N*-methylindole (15%). We argued that the formation of the dimer (**2**) would be suppressed by the removal of hydrogen chloride. We considered a number of scavengers that have been used previously. For example hindered bases such as 2,6-di-*t*-butyl-4-methylpyridine, and dicyclohexyl methylamine, and also propylene oxide. They interact with Lewis acids and inhibit the desired reaction or they do not completely remove the hydrogen chloride. On the other hand, by using bis(trimethylsilyl)acetamide (BTMSA) to remove hydrogen chloride, the two by-products, acetamide and the mild Lewis acid chlorotrimethylsilane, are innocuous. This suggested a second reaction carried out for a longer time (4h) in the presence of the scavenger (3.5 mmol).[5, 11] In this latter case we obtained the compound (**1**) in 90% yield and no dimer (**2**). A third reaction in which *N*-methylindole (10 mmol) was allowed to interact at 0° C with methyl chloromethoxyacetate (4.9 mmol), zinc chloride (5 mmol) and BTMSA (3.5 mmol) for 8h allowed us to isolate the intermediate (**1**) in 60% yield. A sequence of reactions leading to the observed products is shown in the ***Scheme***.



Scheme

(i) MeOH; (ii) MeOCH(Cl)CO_2Me; (iii) HCl; (iv)*N*-methylindole

Similar results were obtained using indole. A reaction of methyl chloromethoxyacetate (5 mmol) with indole (10 mmol) in the presence of BTMSA (5 mmol) and zinc chloride (1.75 mmol) for 18h at room temperature gave the expected product (**4**) in 37% yield together with the regioisomer (**5**) in 4% yield. It is known that BTMSA gives the *N*-trimethylsilyl derivative of indole very easily[12] and this may account for the differences that we have observed as compared with the reactions of *N*-methylindole. In a second experiment carried out at 0° C for 8h in the presence of 100 mol% of zinc chloride we obtained methyl 3,3'-di-indolylacetate (**6**) in 69% yield.



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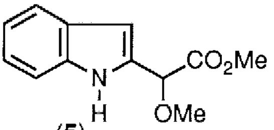

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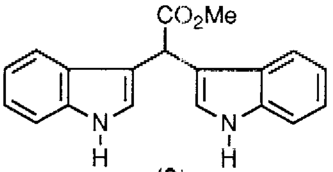
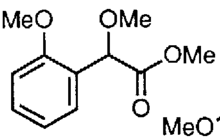


(6)

Reactions using anisole and other methoxybenzene derivatives are interesting in that they show evidence for intramolecular delivery of the electrophile when using tin(IV) chloride as the Lewis acid. Thus a reaction of anisole with methyl chloromethoxyacetate, tin(IV) chloride, and BTMSA in dichloromethane at 20° C for 2h gave a 74% yield of a mixture of methyl α-methoxy-*o*-methoxyphenylacetate (**7**) and methyl α-methoxy-*p*-methoxyphenylacetate (**8**) in a ratio of 6.1:3.9. It was relatively easy to obtain a pure sample of the ester (**7**) by a combination of chromatographic procedures but the regio-isomer (**8**) was only isolated in a pure form after preparative hplc. Although there is little precedent for electrophilic attack at the 2-position in *m*-dimethoxybenzene, we obtained the three products (**10**), (**11**), and (**12**) in isolated yields of 70%, 10%, and 10% from a reaction with methyl chloromethoxyacetate, tin(IV) chloride, and BTMSA in dichloromethane at -40° C for 2h.

A reaction of *p*-dimethoxybenzene was unexceptional and gave the expected product (**13**) in 87% yield together with (**14**) in 8% yield in a reaction carried out at 0° C for 2h. It is noteworthy that a reaction of anisole (3 mol equivalents), methyl chloromethoxyacetate, and tin(IV) chloride (1 mol equivalent) at 0° C for 1h gave the compound (**7**) in 47% yield together with the methyl diarylacetate (**9**) in 47% yield. All of the compound (**8**) was used up. This result suggests that the stability of (**7**) may be related to its ability to co-ordinate with the Lewis acid. Evidence of co-ordination with the oxygen functions is clear from the downfield shifts in the ^{1}H nmr spectrum observed when 1 mol equivalent of tin(IV) chloride is added to the compound (**7**). The observed chemical shifts δ_H and ($\Delta\delta$ values) of the methoxy- groups were 3.77 (0.38), 3.89 (0.16), and 4.12 (0.27), with the aromatic methine signals deshielded by amounts ranging from 0.05 to 0.12 ppm.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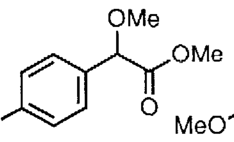
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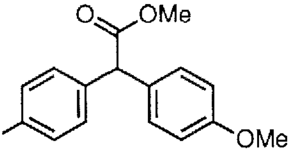
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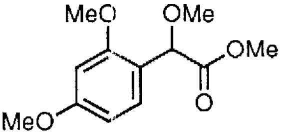
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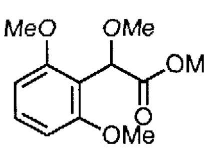
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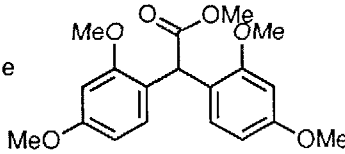
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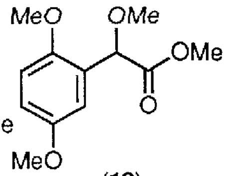
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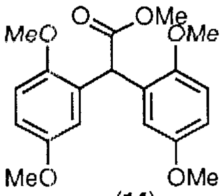
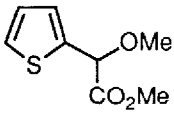

(14)

Reactions with π-excessive heterocycles other than indole are more complex. However, a reaction of methyl chloromethoxyacetate with thiophene and tin(IV) chloride in dichloromethane in the presence of BTMSA at -24° C for 17h gave a mixture of the regioisomers (**15**) and (**16**) in yields of 54% and 6% respectively. It may be anticipated that the isomer (**15**) would afford a reactive cation in the presence of a protic acid more easily than (**16**). In accord with this reasoning a similar reaction carried out at -10° C in the absence of BTMSA gave methyl di-2-thienylacetate (**17**) in 53% yield together with a 10% yield of (**16**). Other products are also formed in these reactions including those containing three and four thiophene residues.

Although it is difficult to suppress the decomposition of furan derivatives a reaction of 2-methylfuran with methyl chloromethoxyacetate using zinc chloride at room temperature in THF for 1h gave the diarylacetate derivative (**18**) in 46% yield while in an otherwise similar reaction in which we added BTMSA we obtained methyl 5-methyl-α-methoxy-2-furylacetate (**19**) in 25% yield.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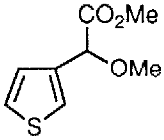
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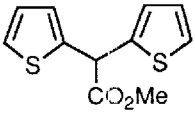
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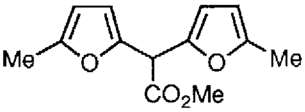
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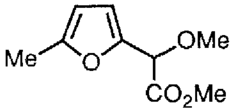
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The available evidence suggests that the reactions that we report involve, in the first step, an S_N2 like reaction where the rate of reaction is determined by the nucleophilicity of the aromatic substrate and by the Lewis acid-methyl chloromethoxyacetate complex. The stereochemical result of this is that racemic methyl chloromethoxyacetate gives a racemic product. On the other hand, our evidence suggests that the reactions leading to methyl diarylacetates proceed via a cationic intermediate which may lead to stereodifferentiation as a result of diastereofacial selectivity. The formation of unusual regio-isomers [compounds (**5**), (**7**), (**11**) and (**16**)] in a number of the reactions reported suggests that the Lewis acid complex of methyl chloromethoxyacetate can also involve the hetero-atom in the aromatic substrate It is our intention to study the reactions in more detail in order to exploit the stereochemical and regiochemical possibilities that are outlined in this communication.

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9. All of the new compounds reported have been fully characterised by either elemental analysis or accurate mass measurements on molecular ions together with high field ^{1}H and ^{13}C nuclear magnetic resonance spectra and appropriate 2-D spectra. Mixtures of products obtained in the reactions reported were easily separated by flash chromatography, except in the case of compound (**8**) where we used preparative hplc. The yields quoted, except in the case of compound (**8**), refer to material isolated after chromatographic separation.
   Examples of data obtained from compounds formed in a single reaction type include n.m.r. spectral data, for compound (**1**) : $\delta_H = 3.4$ (s, Me), 3.70 (s, Me), 3.72 (s, Me), 5.1 (s, 1H), 7.15 - 7.3 (m, 4H), 7.75 (d, $J = 7.5$ Hz, 1H) and $\delta_C = 32.9$ (Me), 52.2 (Me), 56.9 (Me), 76.2 (CH), 109.4 (CH), 109.6 (C), 119.7 (CH), 119.9 (CH), 122.1 (CH), 126.3 (C), 128.5 (CH), 137.1 (C), and 171.7 (C=O); for compound (**2**) : $\delta_H = 2.64$ (s, Me), 3.13 - 3.35 (A-B of ABX), 3.75 (s, Me), 4.57 - 4.65 (X of ABX), 6.5 - 7.3 (m, 8H), 7.68 (d, $J = 7.5$ Hz, 1H) and $\delta_C = 32.7$ (Me), 34.1 (Me), 37.8 (CH_2), 64.7 (CH), 107.2 (CH), 109.2 (CH), 115.1 (C), 117.8 (CH), 119.0 (CH), 120.1 (CH), 121.8 (CH), 124.0 (CH), 126.6 (C), 127.3 (CH), 127.5 (CH), 129.3 (C), 137.5 (C), and 153.3 (C); and for compound (**3**) : $\delta_H = 3.68$ (s, 2 x Me), 3.73 (s, Me), 5.50 (s, 1H),7.00 - 7.29 (m, 8H), 7.62 (d, $J = 8.0$ Hz, 2H) and $\delta_C = 32.7$ (Me), 40.2 (CH), 52.2 (Me), 109.3 (CH), 112.1 (C), 119.1 (CH), 119.3 (CH), 121.7 (CH), 127.0 (C), 127.9 (CH), 137.1 (C), and 174.0 (C=O).
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