Lanthanide Triflate Catalysed Reactions of Acetals with Primary Amines and Cascade Cyclisation Reactions

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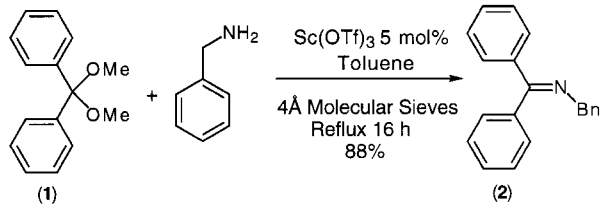
Abstract: The formation of imines from acetals and primary amines can be carried out at significantly lower temperatures using scandium or lanthanide triflates as catalysts, than in the absence of a catalyst: the intermediate aminol ethers can also take part in cascade cyclisation reactions, for example using tryptamine and ethyl tryptophanate.

The use of Lewis acids to promote imine formation of hindered and unreactive ketones, such as aromatic ketones is well known.[1] Examples of imine formation catalysed by zinc chloride,[2a] thallium acetate[2b] and titanium tetrachloride[2c,d] have all been reported. However, Lewis acid chlorides have some disadvantages. In addition to being difficult to handle, they also require the use of more than a stoichiometric amount of the acid chloride and that requires the disposal of substantial quantities of insoluble residues.[3] We observed difficulties in obtaining reproducible yields of some imines from carbonyl compounds that carried other potentially reactive functionalities when using established protocols. The use of rare earth salts, including scandium triflate, has been developed recently in a number of important synthetic operations and a number of the mentioned disadvantages are thereby avoided.[4] More recent applications include Friedel-Crafts alkylation reactions,[5] Michael reactions, including enantioselective examples,[6] reactions involving aldimines,[7] and the formation of enamino esters.[8] Three component coupling reactions catalysed by rare earth triflates have also been studied and include reactions of aldehydes, hydroxylamines, and alkenes that result in the formation of isoxazolidines[9a] and reactions of aldehydes, *N*-benzoylhydrazine and silylenolates that give precursors to pyrazolones.[9b] The formation of a number of *N*-benzylguanidines[10] by the addition of benzylamine to carbodiimide derivatives and trans acetalisation[11] reactions were both found to be catalysed by scandium triflate. These transformations suggested the use of lanthanide triflates in imine formation. We now report herein the use of scandium(III) and some lanthanide triflates in reactions of acetals with primary and secondary amines and some cascade reactions of primary amines with methyl 2-(1,1-dimethoxyethyl)benzoate.

Our initial studies involved imine formation from ketones and primary amines using scandium triflate (5 mol%) in toluene where the water was removed by azeotropic distillation. Whereas benzylamine gave the imine with benzophenone in 67% yield after purification, a number of other reactions gave the products in disappointing yields. Reports that imines can be prepared from acetals have been published over a long period of time.[12] The yields varied from poor to very good (10-95%) but it was invariably found that temperatures in the region of 180-200 °C were required to effect the transformation.

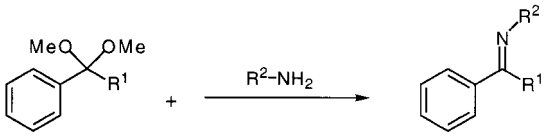
We prepared the range of dimethyl acetals of ketones that we required in excellent yields using methyl orthoformate adsorbed on montmorillonite clay K-10.[13] Although the efficiency of scandium triflate is not reduced by the presence of alcohols we carried out reactions of primary amines under Dean-Stark conditions with 4 Å molecular sieves in the trap. We found that when a solution of benzylamine and benzophenone dimethyl-acetal (**1**) were heated under reflux for 16h in toluene in the presence of 5 mol% of scandium (III) triflate we obtained the expected imine (**2**) in 88% yield after purification. In a control experiment we showed that no imine was formed in the absence of scandium triflate.



Scheme 1

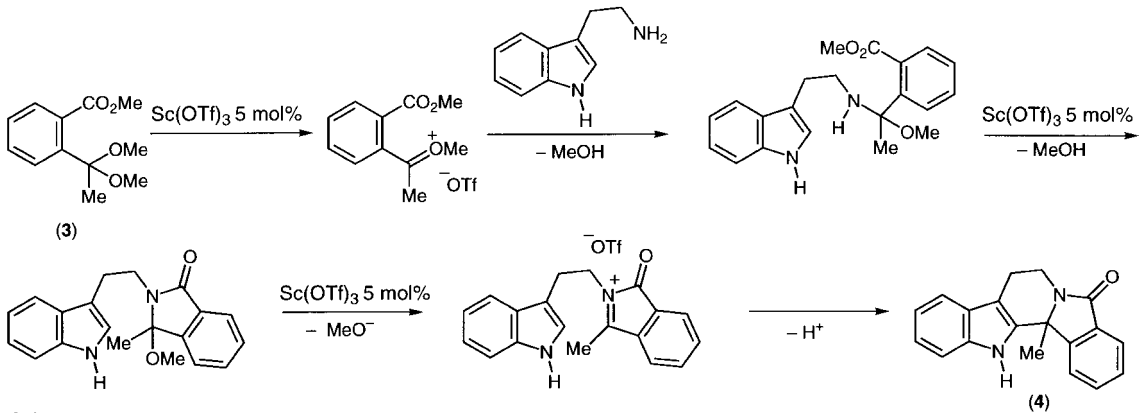
Thus the reaction shown in **Scheme 1** using scandium triflate is truly catalytic whereas reactions using zinc chloride,[2a] thallium acetate[2b] and titanium tetrachloride[2c,d] require stoichiometric amounts of the Lewis acids. Other representative examples of the method are given in the **Table**. We note that the new protocol gave a significant improvement in the yield of the imine derived from benzophenone and (R)-(+)-α-methylbenzylamine as compared to the 45-60% yields reported using titanium (IV) chloride.[14] The yield of the product of the reaction of 4-aminopyridine with benzophenone dimethylacetal was reported to be 32% when the two reactants were heated in a sealed tube for 96h.[12c] Our method gave more than double that. We also carried out reactions using lanthanum, ytterbium, and copper(II) triflates in addition to those reported below. We conclude that there is little to choose between the various triflates in the reactions that we studied.

Table



R^1	Amine	Solvent	Time	Yield
H	aniline	toluene	16h	92%
Me	isopropylamine	toluene	16h	41%
Me	aniline	toluene	16h	89%
Ph	isopropylamine	toluene	16h	96%
Ph	benzylamine	toluene	16h	88%
Ph	(R)-(+)-α-methylbenzylamine	toluene	16h	10%
Ph	(R)-(+)-α-methylbenzylamine	xylene	16h	90%
Ph	4-aminopyridine	xylene	16h	55%
Ph	4-aminopyridine	xylene	96h	76 %

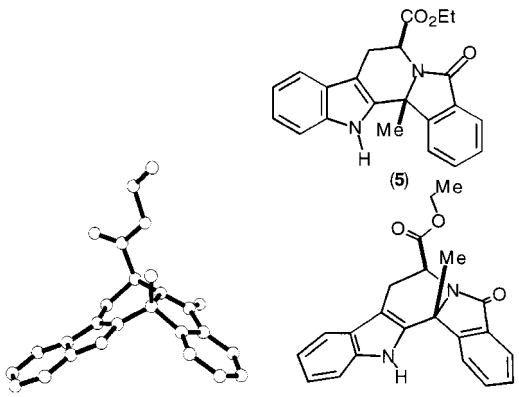
We presumed that the reactions proceed *via* aminol ethers that result from the capture of methoxycarbenium ions by the primary amines and therefore that the reactions could be adapted to take part in a cascade sequence leading to isoindoloisoquinoline derivatives. Although the conversion of 2-acetylbenzoic acid into its methyl ester gives almost quantitative yields using diazomethane,[15] conventional Fischer-Speier procedures were reported to give mixtures that were not separated but in which the pseudo-acid predominated.[16] In our hands, using methanol



Scheme 2

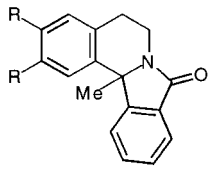
and sulfuric acid, we obtained the pseudo ester in 65% yield together with methyl 2-acetylbenzoate in 29% yield after separation using flash chromatography. However, we found that when the dry potassium salt from 2-acetylbenzoic acid was dissolved in DMSO and methylated with methyl iodide, methyl 2-acetylbenzoate was isolable in 86% yield. Conversion into the related dimethyl acetal, methyl 2-(1,1-dimethoxyethyl)benzoate (**3**) was achieved in 78% yield by using the methyl orthoformate - montmorillonite clay K-10 method.

We had previously shown that imines derived from methyl 2-formylbenzoate undergo base catalysed rearrangement reactions that lead to acyliminium ion precursors and hence cyclised to isoindoloisoquinoline derivatives, for example using titanium tetrachloride.[17] We argued that acetals derived from esters of 2-acylbenzoic acids should undergo cascade sequences with suitable primary amines in the presence of mild Lewis acids. We therefore heated a solution of tryptamine and acetal **3** in toluene for 16 h in the presence 10 mol% of scandium triflate and 4Å molecular sieves. We isolated the β-carboline derivative **4**[18] in 91% yield, presumably as a result of the sequence of reactions shown in **Scheme 2**. Although the ethyl ester of tryptophane is less basic than tryptamine we investigated the reaction with the acetal **3**. The compound **5** which was isolated as a single diastereomer in 36% yield. In one experiment methyl 2-acetylbenzoate was also recovered in 48% yield after an aqueous work-up. An X-ray crystal structure determination showed that both the ethyl ester and methyl groups occupy axial positions on the same face of the molecule.[19]

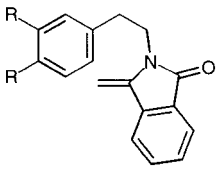


*X-Ray structure representation of the compound (**5**)*

In an experiment using acetal **3** together with 3,4-dimethoxy-β-phenylethylamine we obtained the anticipated cascade product **6** in 54% yield together with 3-methyleneisoindol-1-one derivative **7** in 16% yield. It is possible in this case that the compound **7** is an intermediate involved in the cascade sequence. We found that when the compound **7** was heated under reflux in xylene for 16h in the presence of 10 mol% of scandium triflate we isolated the compound **6** in 81% yield. As expected, replacement of the more nucleophilic arylethylamines by β-phenylethylamine did not lead to the final cascade product in the presence of scandium triflate; the product **8** was isolated in 75% yield. On the other hand the final cyclisation product **9** was obtained in 67% yield when the 3-methyleneisoindol-1-one **8** was heated in the presence of orthophosphoric acid.



(**6**, R = OMe)
(**9**, R = H)



(**7**, R = OMe)
(**8**, R = H)

Typical Experimental Procedure

Trimethyl orthoformate (5 ml, 46 mmol), montmorillonite clay K-10 (3g), and methyl 2-acetylbenzoate (1.5g, 8 mmol) gave, after stirring for 16 h, methyl 2-(1,1-dimethoxyethyl)benzoate (**3**)[20] (1.48g 78%) as a colourless oil. Scandium triflate (0.12g, 0.25 mmol) was added to a solution of methyl 2-(1,1-dimethoxyethyl)benzoate (0.56g, 2.5 mmol) and 3,4-dimethoxy-β-phenylethylamine (0.45g, 2.5 mmol) in xylene (30 ml). The reaction mixture was heated under reflux using a Dean-Stark trap containing activated molecular sieves (4Å) for 16 h, filtered and the solvent evaporated under reduced pressure. Chromatography on silica gel, eluting with ethyl acetate : light petroleum (2 : 1), gave the compounds **6**[21] (0.415g, 54%), a yellow solid, m.p. 197-200 °C, and **7**[22] (0.12g, 16%), a pale yellow solid, m.p. 138-141 °C.

Acknowledgements. We thank the EPSRC and SmithKline Beecham for a CASE award (to MTS) .

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20. New compounds have been fully characterised by elemental analysis or accurate mass measurement of the mass spectrometric molecular ion and other spectroscopic data.
$M^{+\cdot}$ 223.9827; $C_{12}H_{16}O_4$ requires M 224.1049; ν_{max} 2950, 2833, 1732 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.64 (s, 3H), 3.13 (s, 6H), 3.83 (s, 3H), 7.26-7.45 (m, 3H), and 7.46-7.48 (m, 1H) ppm; δ_C (100 MHz, $CDCl_3$) 25.1 (Me), 49.0 (2 x OMe), 51.1 (OMe), 102.2 (C), 126.8 (CH), 127.7 (CH), 129.2 (CH), 132.9 (C), 140.2 (C), and 171.2 (C=O) ppm.
21. $M^{+\cdot}$ 309.1368; $C_{19}H_{19}NO_3$ requires M 309.1364; ν_{max} 2939, 1681 cm^{-1}; δ_H (250 MHz, $CDCl_3$), 1.81 (s, 3H), 2.72 (m, 1H), 3.04 (dxdxd, 1H, *J* = 16.0, 11.9, 6.5 Hz), 3.37 (dxdxd, 1H, *J* = 13.1, 11.9, 4.5 Hz), 3.82 (s, 3H), 3.94 (s, 3H), 4.62 (dxdxd, 1H, *J* = 13.1, 6.5, 1.2 Hz), 6.58 (s, 1H), 7.18 (s, 1H), 7.45 (t, 1H, *J* = 7.4 Hz), 7.72 (dxt, 1H, *J* = 7.5 and 1.1 Hz), and 7.83-7.87 (m, 2H), ppm; δ_C (62.9 MHz, $CDCl_3$) 28.7 (Me), 29.2 (CH_2), 35.0 (CH_2), 55.8 (OMe), 56.3 (OMe), 63.6 (C), 109.5 (CH), 112.0 (CH), 122.2 (CH), 123.8 (CH), 125.8 (C), 128.2 (CH), 130.9 (C), 131.1 (C), 131.9 (CH), 147.7 (C), 148.2 (C), 150.7 (C), and 167.4 (C=O) ppm.
22. $M^{+\cdot}$ 309.1366; $C_{19}H_{19}NO_3$ requires M 309.1364; ν_{max} 2940, 1663 cm^{-1}; δ_H (250 MHz, $CDCl_3$), 2.89-2.97 (m, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 3.91-3.98 (m, 2H), 4.82 (d, 1H, *J* = 2.4 Hz), 5.18 (d, 1H, *J* = 2.4 Hz), 6.73 (s, 1H), 6.79 (m, 2H), 7.45-7.60 (m, 2H), 7.66-7.72 (m 1H), and 7.80-7.84 (m, 1H), ppm; δ_C (62.9 MHz, $CDCl_3$), 34.0 (CH_2), 41.1 (CH_2), 55.8 (OMe), 55.9 (OMe), 88.7 (CH_2), 111.4 (CH), 112.1 (CH), 119.8 (CH), 120.8 (CH), 123.1 (CH), 129.5 (CH), 131.0 (C), 131.9 (CH), 133.8 (C), 136.6 (C), 141.7 (C), 147.7 (C), 149.0 (C), and 166.9 (C=O) ppm.