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FLUORIDE-CATALYZED INTRAMOLECULAR DENITROCYCLIZATION OF NITROTOLUENES TO INDANES

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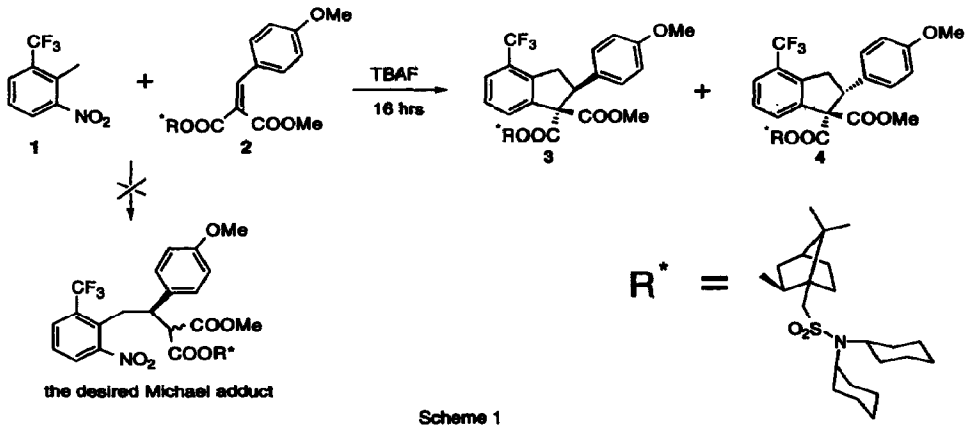
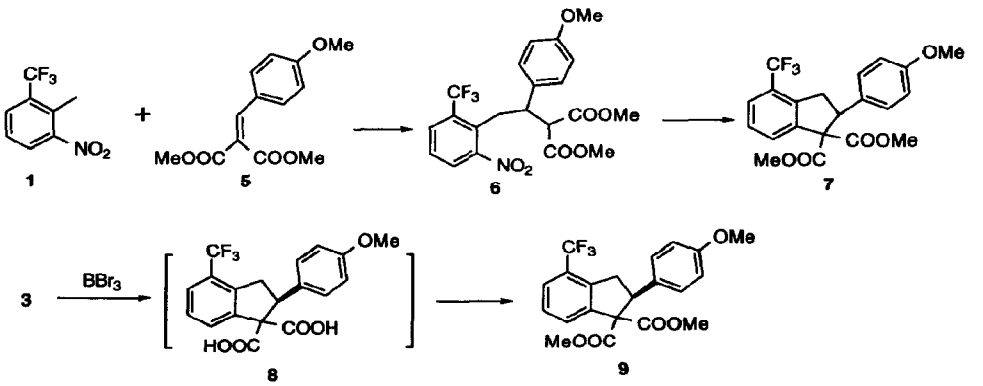
Abstract: Fluoride-catalyzed Michael addition of nitrotoluenes to α,β-unsaturated esters followed by subsequent denitrocyclization to indanes is described.

As part of a program directed towards the preparation of calcium channel blockers,[1] we developed a mild and efficient methodology for the stereoselective construction of chiral benzazepines using tetrabutylammonium fluoride[2] as the catalyst. During the course of our search for a suitable chiral auxiliary for this transformation, camphorsulfon-amide[3] was investigated as a possible directing group for the stereoselective Michael addition of nitrotoluenes to chiral α,β-unsaturated esters. Thus, reaction of **2** and nitrotoluene **1** in the presence of tetrabutylammonium fluoride, molecular sieves, and potassium carbonate in THF at room temperature[4] for 16 hrs gave a 4:1 mixture of chiral indanes **3**[5] and **4** in a combined yield of 70% yield without any detectable amount of the desired Michael adduct (Scheme 1).



Scheme 1

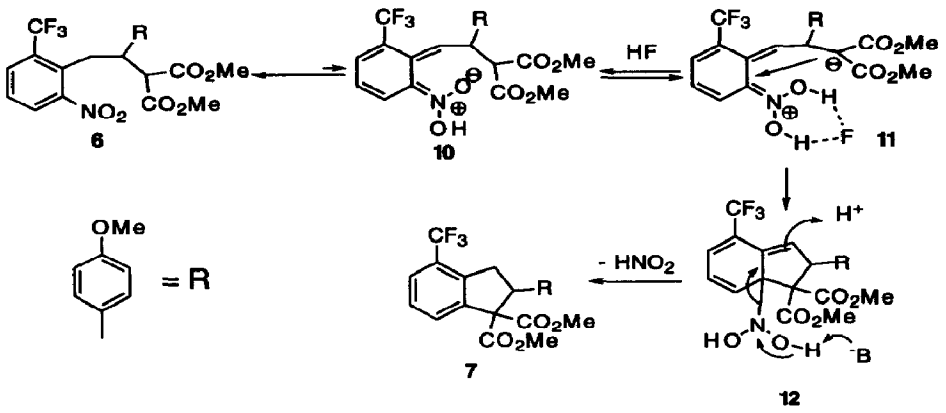
Reaction of α,β-unsaturated ester **5** and nitrotoluene **1** in the presence of tetrabutylammonium fluoride, molecular sieves, and anhydrous K_2CO_3 in THF at 0°C followed by warming to room temperature for 30 minutes gave the Michael adduct **6** in 90% isolated yield. Subsequent reaction of **6** (isolated and purified) with tetrabutylammonium fluoride in the presence of molecular sieves in THF at room temperature for 16 hrs gave indane **7** in 65% isolated yield (Scheme 2). In fact, reaction of **5** and **1** at room temperature under the above conditions directly gave rise to indane **7** in 60% isolated yield. Reaction of **3** with BBr_3 followed by CH_2N_2 treatment gave **9** ($[\alpha]_D$ -11.8; c=1, $CHCl_3$), the optically active form of **7**.



Scheme 2

The mechanism of this indane formation is speculative at this point. However, reaction of **6** with NaH did not give any indane, thus ruling out the possibility of an intramolecular displacement reaction of the malonate anion of **6**. Addition of tetrabutylammonium bromide to the above NaH reaction also did not give any indane. Only tetrabutylammonium fluoride promoted the formation of indane **7** from **6**. Thus, it was demonstrated that fluoride ion appeared necessary for the indane formation.

It is plausible that nitrotoluene is tautomerized to its aci-form **10** (Scheme 3), as proposed by Bergman[6] and coworkers. The key role of fluoride ion (or the incipient HF[7]) involves stabilizing the aci-form of the nitrotoluene, allowing anion formation of the malonate moiety and subsequent attack on the activated nitro group. The resulting intermediate **12** is then converted to **7** via the expulsion of nitrous acid and, finally, aromatization. The overall proposed scheme resembles the well-known Nef[8] reaction for the transformation of nitro compounds to the corresponding ketones.



Scheme 3

To the best of our knowledge, there is no precedent for the intramolecular C-denitrocyclization[9] mediated by fluoride ion. Although it is not clear how general this reaction may be for the production of differently substituted indanes, the synthesis of **3** and **9** is efficient and highly stereoselective and suggests interesting possibilities for the preparation of other chiral indane derivatives.

The experimental procedure for the formation of indanes **3** and **4** is as follows: A mixture of n-$BuN_4F \cdot x\ H_2O$ (4.22 gms), 4 Å molecular sieves (24 gms), and K_2CO_3 (4 gms) was vigorously stirred in THF (40 ml) at room temperature for 30 minutes. To this slurry was added 6-trifluoromethyl-2-nitrotoluene (2.1 ml, 2.0 eq) followed by dropwise addition of a solution of α,β-unsaturated ester **2** (4.13 gms, 6.72 mmole) in THF (10 ml) over a period of 10 minutes. The resulting brown slurry was stirred vigorously for 16 hrs at room temperature. It was quenched with 30% aqueous acetic acid (~3 ml) and diluted with EtOAc (80 ml). The solid residue was removed by filtration and the organic solution was washed with sat'd $NaHCO_3$ (15 ml x 1), brine (20 ml x 2), dried over $MgSO_4$, filtered, and concentrated. Column chromatography over silica gel (2% EtOAc in benzene as eluent) afforded 3.0 gms (54% yield) of **3** and 0.78 gms (14% yield) of **4**.[10]

Application of a similar procedure provided indane **9** [10] as an oil in 54% yield after column chromatographic (over silica gel, 6% EtOAc in benzene as eluent) purification.

Acknowledgment:

We thank Drs. R. Mueller, D. Kronenthal, and D. Floyd for their helpful discussions.

References:

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10. Compounds **3**, **4**, and **9** have the following physical and spectroscopic characteristics:

3, White solid, m.p. 188-190°C; $[\alpha]_D$ +68.8 (c 1.0, $CHCl_3$); TLC (Et_2O:hexane, 3:7) R_f = 0.4; HNMR ($CDCl_3$) δ 7.75 (d, 1H, J = 8.2 Hz), 7.60 (d, 1H, J = 8.2 Hz), 7.36 (t, 1H, J = 8.2 Hz), 6.88 (d, 2H, J = 8.6 Hz), 6.68 (d, 2H, J = 8.6 Hz), 4.84 (dd, 1H, J = 11.4 & 3.4 Hz), 4.63 (dd, 1H, J = 11.4 & 2.0 Hz), 3.72 (s, 3H), 3.66 (t, 1H, J = 8.2 Hz), 3.37 (s, 3H), 3.36-3.25 (m, 3H), 3.23 (d, 1H, J = 14 Hz), 2.66 (d, 1H, J = 14 Hz), 2.10-1.0 (m, 27H), 0.83 (s, 3H), 0.65 (s, 3H).

4, White solid, m.p. 104-106°C; $[\alpha]_D$ +24.4 (c 1.0, $CHCl_3$); TLC (Et_2O:hexane, 3:7) R_f = 0.16; HNMR ($CDCl_3$) δ 7.75 (d, 1H, J = 7.7 Hz), 7.60 (d, 1H, J = 7.7 Hz), 7.34 (t, 1H, J = 7.7 Hz), 7.01 (d, 2H, J = 8.7 Hz), 6.71 (d, 2H, J = 8.7 Hz), 4.64 (dd, 1H, J = 3.2 & 5.5 Hz), 4.56 (dd, 1H, J = 5.2 & 2.8 Hz), 3.73 (s, 3H), 3.70 (s, 3H), 3.63 (t, 1H, J = 8.2 Hz), 3.43-3.35 (m, 3H), 3.18 (d, 1H, J = 13.8 Hz), 2.69 (d, 1H, J = 13.8 Hz), 2.17-0.88 (m, 27H), 0.84 (s, 3H), 0.60 (s, 3H).

9, oil; TLC (Et_2O:hexane, 3:7) R_f = 0.20; HNMR ($CDCl_3$) δ 7.76 (d, 1H, J = 7.8 Hz), 7.62 (d, 1H, J = 7.8 Hz), 7.40 (t, 1H, J = 7.8 Hz), 7.00 (d, 2H, J = 8.7 Hz), 6.73 (d, 2H, J = 8.7 Hz), 4.54 (dd, 1H, J = 4.4 & 6.3 Hz), 3.76 (s, 3H), 3.74 (s, 3H), 3.69 (t, 1H, J = 8.6 Hz), 3.40 (dd, 1H, J = 2.8 & 10.0 Hz), 3.33 (s, 3H).

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