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Novel triethylamine mediated thermal reactions of 3-aryl-2-cyanoprop-2-enoic acid derivatives—demethylation, reduction and vinylogation

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ABSTRACT

3-Aryl-2-propenoic acid derivatives undergo interesting reactions with hot triethylamine. Substrates like **6** having a methoxyl with a nitro in the *ortho* and cyanoacrylic derivatives in the *para* positions give O-demethylated products, for example, entacapone **7**. On the other hand compounds like **16** having the NO_2 in the *para* and cyanoacrylic in the *ortho* position undergo reduction and vinylogation. The latter phenomenon is observed in the absence of the NO_2 group also.

The reduction of electron deficient systems by triethylamine under photolytic conditions is well documented and postulated to go through a radical mechanism.[1] There have been very few examples of triethylamine exhibiting reductive properties under thermal conditions. The reaction of triethylamine with trifluoroacetyl fluoride **1** leads to the aldehyde **2** and vinyl amine **3** (Scheme 1).[2a] In all such reactions triethylamine acts as a hydride donor getting itself oxidized to *N*-vinyldiethylamine.[1b]

The thermal oxidation of triethylamine by naphthoquinones like dichlone **4** leading to the formation of **5**, falls in this category.[3] The reaction occurs by triethylamine getting oxidized to *N*-vinyldiethylamine which then substitutes the chlorine atom in **4** (Scheme 2).

We have come across some interesting and unexpected outcomes in the reaction of triethylamine with arylidenecyanoacetic acid derivatives which we report now.

The serendipitous findings were made during our successful exercises on a new synthesis of the catechol-*O*-methyltransferase (COMT) inhibitor entacapone **7** by mild demethylation of the precursor **6** by hot ethanolic triethylamine. The approach was designed to take advantage of the vulnerability of a methyl moiety as part of an aromatic methoxyl group carrying electron withdrawing groups at *ortho* (NO_2) and *para* (acrylic derivatives) position (Scheme 3).[4] In a typical experiment, a solution of **6** in ethanol containing triethylamine was heated at 70–75 °C for 12 h and the product **7** obtained by evaporation, acidification with dilute hydrochloric acid and crystallization from ethylacetate. Since **6** is made readily from 5-nitroisovanillin and *N*,*N*-diethylcyano acetamide, the process constitutes a new synthesis of entacapone under mild conditions. Demethylation occurred in this case by nucleophilic attack on the methyl group as shown by us in one experiment wherein the crude product from triethylamine reaction containing the salt of **7** was deliberately neutralized with cold, dilute HI to enable us to capture the methyl triethylammonium counter ion as the easily characterized quaternary iodide. Such demethylation proceeded in 45–58% yields, on analogues **8**, **10** and **12** and was extended to substrates including only one methoxyl and *ortho* nitro group **14**. All reported syntheses of entacapone[5] use harsh conditions of O-demethylation such as aluminium chloride, boiling HBr and thiophenoxide at high temperatures on substrates at an early or late stage in the synthetic route. Diethylamine and piperidine also bring about demethylation in similar yields. Treatment of **6** with diethylamine in ethanol at 55–60 °C and piperidine in

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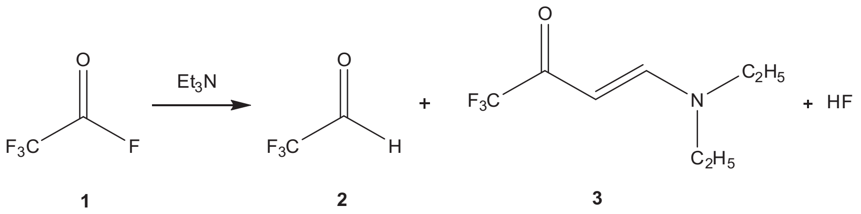
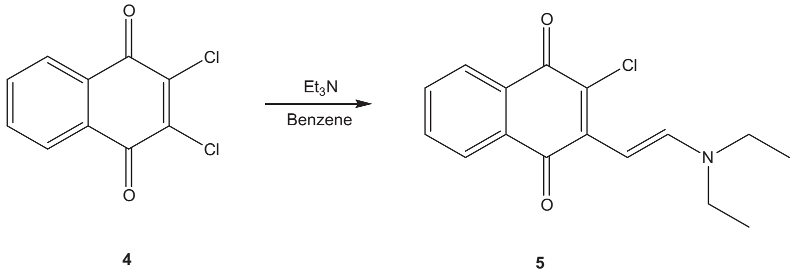
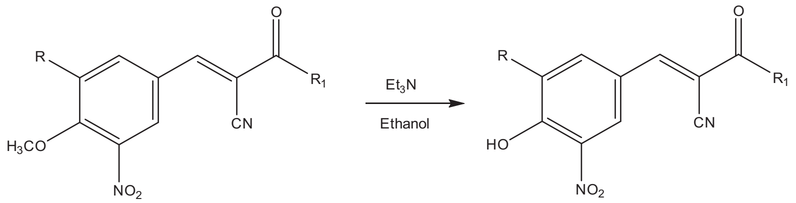


Scheme 1.



Scheme 2.

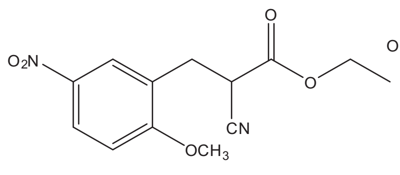


6: R=OH;R$_1$=N(CH$_2$CH$_3$)$_2$	7: R=OH; R$_1$ =N(CH$_2$CH$_3$)$_2$
8: R=OH; R$_1$=OCH$_2$CH$_3$	9: R=OH; R$_1$= OCH$_2$CH$_3$
10: R=OCH$_3$; R$_1$=N(CH$_2$CH$_3$)$_2$	11: R=OCH$_3$; R$_1$=N(CH$_2$CH$_3$)$_2$
12: R=OCH$_3$; R$_1$=OCH$_2$CH$_3$	13: R=OCH$_3$; R$_1$=OCH$_2$CH$_3$
14: R=H; R$_1$=OCH$_2$CH$_3$	15: R= H; R$_1$=OCH$_2$CH$_3$

Scheme 3.

ethanol at 55–60 °C for 12 h afforded **7** in 40% and 47%, respectively. Further experiments to optimize yields will study other solvents among various parameters.

In trying to unravel the scope of the demethylation we subjected the regioisomer **16** of **14** to reaction with triethylamine in ethanol at 70–75 °C for 12 h.



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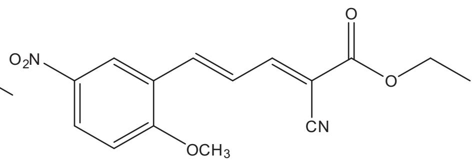

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The reaction surprisingly did not lead to demethylation, but gave a mixture of two compounds **17** (48%) and **18** (48%) and starting material (3%) by NMR analysis. Separation of the mixture by silica gel chromatography afforded the dihydro derivatives **17** mp 111–112 °C; MS *m*/*z* 277.1(negative mode) in isolated yield of 40%, characterized in the ^{1}H NMR spectrum by the absence of the ene proton at δ 8.62 ppm and the appearance of a cluster of signals with an ABX pattern in the region 3-4 ppm characteristics of the CH$_2$–CH present in **17** at δ 3.22 (dd, J = 8.5, 13.7 Hz, 1H), 3.40 (dd, J = 6.8, 13.7 Hz, 1H) and 3.92 (dd, J = 8.5, 6.5 Hz, 1H). This sample was identical with the product obtained by treating **16** with sodium borohydride in ethanol.

The other product **18** differed from **16** in having an additional –CH═CH– in the MS *m*/*z* 301.8 (negative mode) and was established to be **18**[6] mp 186–187 °C. The ^{1}H NMR spectrum had the diagnostic peaks for the newly introduced –CH═CH–CH═ in the aryl region between 7.40–7.55 ppm, δ 7.47 (dd, J = 10.6, 15.2 Hz, 1H) and 7.53