Convenient Synthesis of 4-Nitrotetralones by Selective Side-chain Nitration of Methyl-substituted Acryloylbenzenes, followed by Intramolecular Michael Reaction

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Reaction of polymethyl-substituted acryloylbenzenes (**1**) with fuming nitric acid in acetic anhydride gave the products (**2**) derived from selective side-chain nitration at the *ortho*-position; the subsequent intramolecular Michael reaction leads to exclusive formation of 4-nitrotetralones (**3**).

The synthesis of tetralones, key intermediates for the synthesis of various drugs and natural products, has attracted much attention.[1] We report herein a very efficient, two-step method for the synthesis of 4-nitrotetralone derivatives (**3**) from polymethyl-substituted acryloylbenzenes (**1**).

Reaction of acryloylbenzenes (**1a—h**) with two mol. equiv. of fuming nitric acid in acetic anhydride at 0—5 °C for 2 h gave the corresponding 2-nitromethylacryloylbenzenes (**2a—h**) as the sole isolable product, suggesting that the acryloyl group could effectively direct the side-chain nitration at the *ortho*-position.† The exception was the reaction of (**1b**), in which the formation of (**2b**) was accompanied by vinyl group nitration products (Table 1).

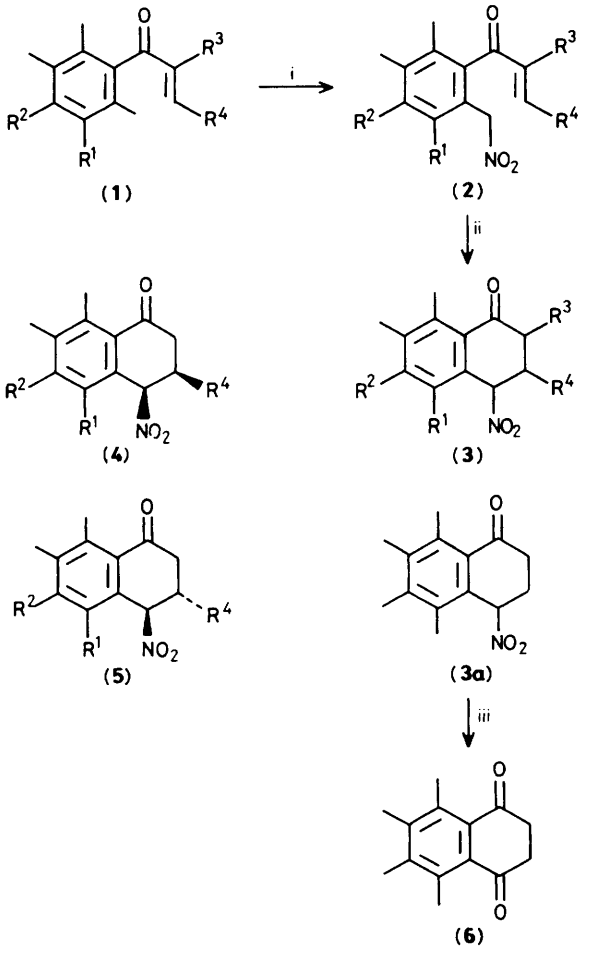
Treatment of (**2a—h**) with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) or triethylamine (TEA) in dichloromethane at room temperature or in refluxing ethanol for 24 h, gave exclusively the corresponding 4-nitrotetralones (**3a—h**) (Table 2), demonstrating that the intramolecular Michael reaction proceeds very smoothly. The reaction of (**2e—h**) with a base resulted in the two stereoisomers, *cis*-(**4**) and *trans*-(**5**).

Table 1. Nitration of (**1a—h**).[a]

Product[b]	Isolated yield/%
(**2a**)	51
(**2b**)	23
(**2c**)	55
(**2d**)	64
(**2e**)	71
(**2f**)	68
(**2g**)	55
(**2h**)	60

[a] Reaction conditions: 99% nitric acid (2 equiv.) in acetic anhydride, 0—5 °C, 2 h. [b] All new compounds gave satisfactory n.m.r., i.r., and mass spectral data and elemental analysis.

† A mechanism for the side-chain nitration of acylpolymethylbenzenes with fuming nitric acid in acetic anhydride has been discussed in our previous paper.[2] The selective formation of 2-nitromethyl compounds in the nitration of 2,4,5,6-tetramethylacylbenzenes can be explained by an enhancement of the reactivity of the 5-position owing to the additivity of substituent effects. In addition, HMO calculations using the parameters reported for oxygen atom and for methyl group in the inductive model show that the order of HOMO electron density on the ring carbons of 2,5,6-trimethyl-4-methoxyacryloylbenzene (**1c**) is 5- > 2- > 6- > 3- > 4- > 1- > vinyl carbons.



a; $R^1 = R^2 = Me$, $R^3 = R^4 = H$
b; $R^1 = R^2 = R^3 = Me$, $R^4 = H$
c; $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
d; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = CO_2Et$
e; $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Ph$
f; $R^1 = R^2 = R^4 = Me$, $R^3 = H$
g; $R^1 = R^3 = H$, $R^2 = Me$, $R^4 = Ph$
h; $R^1 = R^3 = H$, $R^2 = OMe$, $R^4 = Ph$

Scheme 1. *Reagents and conditions*: i, 99% HNO_3 (2 equiv.), acetic anhydride, 0—5 °C, 2 h; ii, DBU (or TEA) (0.1 equiv.), CH_2Cl_2 (or EtOH), reflux (**2c, e, g, h**), 24 h; iii, KOH–MeOH, then $KMnO_4$, $MgSO_4$, H_2O, 0 °C.

Table 2. Intramolecular Michael reaction of (**2a—h**).

Reactant[a]	Product[b] (isolated yield/%)	(**4**) : (**5**)[c]
(**2a**)	(**3a**) (73)	—
(**2b**)	(**3b**) (74)	—
(**2c**)[d]	(**3c**) (60)	—
(**2d**)[e]	(**3d**) (60)	0 : 100
(**2e**)[d]	(**3e**) (51)	40 : 60
(**2f**)	(**3f**) (69)	36 : 64
(**2g**)[d]	(**3g**) (89)	67 : 33
(**2h**)[d]	(**3h**) (80)	72 : 28

[a] Reaction conditions: DBU (0.1 equiv.), CH_2Cl_2, room temp., 24 h. [b] All new compounds gave satisfactory n.m.r., i.r., and mass spectral data and elemental analysis. [c] Determined from h.p.l.c. peak area after calibration using an authentic sample. [d] Solvent EtOH, reflux. [e] Base TEA.

The yields for each step are excellent and, moreover, the nitro group of (**3**) could be easily converted into other functional groups.[3,4] This two-step method consisting of side-chain nitration and subsequent intramolecular Michael reaction, should prove to be valuable for the synthesis of various tetralone and naphthalene derivatives. For example, treatment of (**3a**) with methanolic potassium hydroxide followed by oxidation with an aqueous solution of $KMnO_4$ and $MgSO_4$ at 0 °C gave 5,6,7,8-tetramethyldihydronaphthalene-1,4-dione (**6**) in quantitative yield.

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