Reaction of Carbanions with N-Tosyloxyphthalimide. Formation of 3,3-Disubstituted Quinoline-2,4-diones

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The reaction of a series of carbanions, including both aromatic anions and enolate anions, with N-tosyloxyphthalimide gave 3,3-disubstituted quinoline-2,4-diones. A multi-step mechanism which involves attack of the carbanion on a carbonyl group, ring opening, Lossen-like rearrangement, intermolecular proton transfer, and ring closure is suggested.

The title reaction was studied in order to determine whether N-tosyloxyphthalimide and other imides carrying leaving groups on nitrogen can serve as electrophilic aminating reagents. This amination method [generalized in Equation (1)] has been studied extensively in recent years and now constitutes a well established synthetic method.[1]

$$Nu^- + H_2N{-}X \longrightarrow Nu{-}NH_2 + X^- \qquad (1)$$
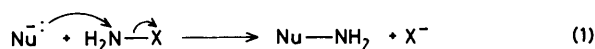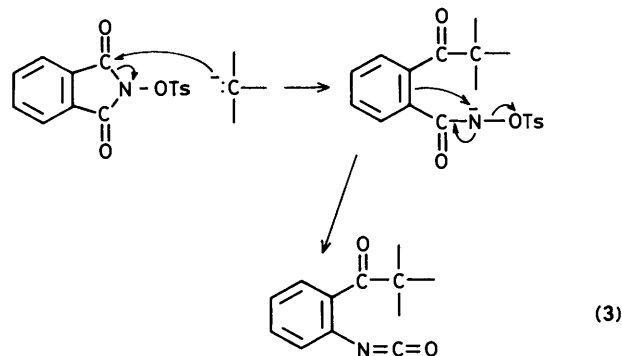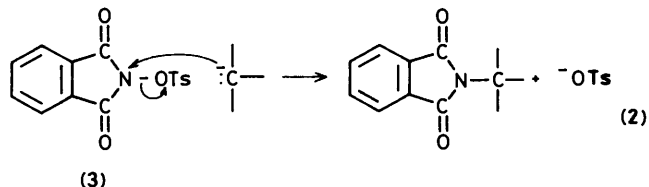
(X = leaving group)

The use of the method for the preparation of primary amines (Nu = carbanion) is limited, as the aminated carbon has to be more acidic than the reagent and thus highly basic carbanions (e.g. the fluoren-9-yl anion) are not aminated.[2] Elimination of this serious restriction can obviously be achieved by design of non-acidic reagents. One approach, well demonstrated by Beak,[3] involves changes in the nature of the leaving group X. Another possibility, tried here, is the use of amination reagents in which both acidic hydrogens are replaced by removable protecting groups.

Our initial experiments in this direction involved attempted dibenzyl-aminations with N,N-dibenzyl-O-tosylhydroxylamine (1). It was found that unlike the reactions of the corresponding dimethyl and diethyl derivatives, which result in dialkyl-amination,[4] the reaction of (1) with a series of carbanions led always to elimination to the Schiff base (2).[5] These reactions yielded the starting carbon acids, benzaldehyde, and benzyl-amine, formed by the hydrolysis of (2) during work-up.
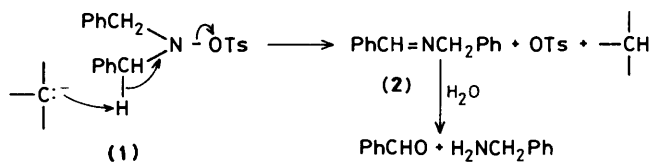
In order to avoid the problem of competing elimination we turned to the reaction of carbanions with N-tosyloxy-phthalimide (3). Reaction according to Equation (2) would produce N- substituted phthalimides which can be easily transformed to primary amines. It was, however, reported[6] that phenoxides and thiophenoxides attack imides similar to (3) at a carbonyl group, with subsequent ring opening and Lossen-like rearrangement. This pathway [Equation (3)] would in our case lead to ortho-isocyanato ketones which can also serve as synthetic intermediates, particularly in the field of fused heterocycles.

The first carbanion tried was the fluoren-9-yl anion (gener-

ated from fluorene and butyl-lithium). Its reaction with (3) (THF, −70 °C) yielded a single product in ca. 40% yield. The product composition ($C_{21}H_{13}NO_2$) indicated combination of the elements of fluorene and phthalimide. It showed i.r. carbonyl absorptions at 1 650 and 1 690 cm^{-1} and the ^1H n.m.r. spectrum lacked any signals at a field higher than 7 p.p.m. The spectral data rule out the possibility of it being either of the primary products according to equation (2) or (3) [compounds (4) and (5) respectively]. The data are, however, in accord with the spiro structures (8) and (9) which can result from them. Both possible primary products (4) or (5) should be more acidic than fluorene, and thus would quench the starting fluorenyl anion to give anions (6) and (7). Anion (6) would then be transformed to (8) by a known[7] rearrangement of α-phthalimido carbanions and anion (7) would cyclise to the dione (9).

It became clear at this stage that a double anionic reaction is involved, and, accordingly, the reaction was carried out using 2 equiv. of the fluorenyl anion, and the yield was indeed almost doubled (75%).

The question as to whether the product is the isoquinoline derivative (8) or the quinoline derivative (9) was settled by a single crystal X-ray analysis. The true structure was established as (9), formed through attack of the fluorenyl anion at a carbonyl group in compound (3), according to Equation (3). Compound (9) is very sensitive to aqueous base, and this caused hydrolytic cleavage of the C(3)—C(4) bond of the quinoline to give the anthranilic acid derivative (10), which, as expected,[8]

Table 1. Positional parameters and estimated standard deviations for compound (9).

Atom	x	y	z	Atom	x	y	z
O(1)	0.402 0(1)	0.436 5(2)	0.388 0(1)	C(10)	0.528 5(2)	0.085 6(3)	0.173 8(3)
O(2)	0.417 1(1)	0.604 8(2)	0.040 0(1)	C(11)	0.447 3(2)	0.007 7(3)	0.117 9(3)
N	0.529 2(1)	0.562 5(2)	0.375 6(1)	C(12)	0.359 7(2)	0.074 5(3)	0.093 3(2)
C(1)	0.273 3(2)	0.324 0(2)	0.110 3(2)	C(13)	0.411 9(1)	0.467 4(3)	0.201 8(2)
C(2)	0.304 9(1)	0.465 3(2)	0.155 8(2)	C(14)	0.446 5(2)	0.489 6(3)	0.329 6(2)
C(3)	0.242 4(2)	0.580 0(3)	0.156 9(2)	C(15)	0.584 4(1)	0.627 1(3)	0.315 8(2)
C(4)	0.146 6(2)	0.550 5(4)	0.113 5(3)	C(16)	0.670 7(2)	0.692 5(3)	0.375 2(2)
C(5)	0.114 6(2)	0.409 0(4)	0.068 7(3)	C(17)	0.726 2(2)	0.755 9(3)	0.317 8(2)
C(6)	0.176 6(2)	0.295 6(3)	0.065 7(3)	C(18)	0.696 5(2)	0.754 6(3)	0.201 1(2)
C(7)	0.354 5(2)	0.224 4(3)	0.124 3(2)	C(19)	0.610 0(2)	0.693 8(3)	0.142 1(2)
C(8)	0.436 7(2)	0.303 5(3)	0.179 0(2)	C(20)	0.553 0(1)	0.629 8(3)	0.198 6(2)
C(9)	0.524 5(2)	0.236 3(3)	0.205 7(2)	C(21)	0.457 7(2)	0.572 8(2)	0.137 4(3)

Estimated standard deviations in the least significant digits are shown in parentheses.

Table 2. Selected bond lengths (Å) and angles (°) for compound (9)

C(1)–C(7)	1.463(3)	C(2)–C(1)–C(7)	109.2(2)
C(2)–C(13)	1.518(2)	C(1)–C(7)–C(8)	109.1(2)
C(8)–C(13)	1.541(3)	C(2)–C(13)–C(8)	101.9(2)
C(13)–C(14)	1.533(2)	C(2)–C(13)–C(14)	111.2(2)
C(13)–C(21)	1.531(3)	C(2)–C(13)–C(21)	113.7(2)
C(14)–N	1.349(2)	C(8)–C(13)–C(14)	107.2(2)
C(15)–N	1.401(3)	C(8)–C(13)–C(21)	107.2(2)
C(20)–C(21)	1.474(2)	C(14)–C(13)–C(21)	114.7(2)
O(1)–C(14)	1.230(2)	C(13)–C(21)–C(20)	116.9(2)
O(2)–C(21)	1.212(2)	C(14)–N–C(15)	125.5(2)
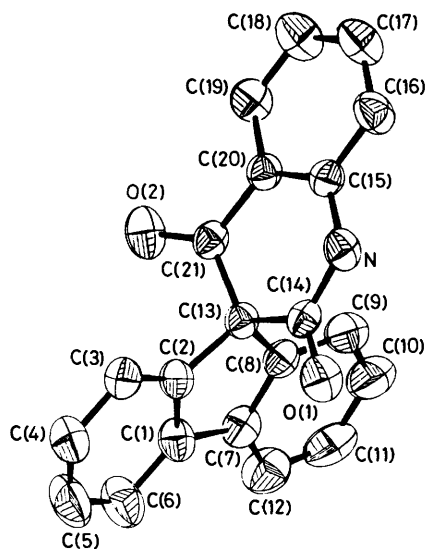
Figure. Molecular structure of compound (9)

underwent cyclization with acetic anhydride to the benzoxazine (11).

In order to check the generality of the process, compound (3) was treated with several other carbanions. The inden-1-yl anion reacted in the same manner as the fluoren-9-yl anion, and gave (12) in 63% yield. The hydrogens at positions 2 and 3 of the indene appeared in the n.m.r. spectrum as doublets at 6.58 and 7.06 p.p.m. (*J* 5.7 Hz), thus supporting the spiro structure. The next substrate tried was ethyl 2-pyridylacetate. As expected, the quinoline (13) was obtained, albeit in lower yield (38%).

(13)

Among the ketones tried, the enolate anion of α-tetralone (generated with LDA) gave (14) smoothly. However, the cyclohexanone product (15) was unstable, and during work-up partly hydrolysed to the acid (16). Treatment of the crude product mixture with aqueous NaOH converted it all quantitatively to (16), which exists completely in the enol form. This was evident from the twofold reaction with diazomethane, which gave the ester (17).

(14)

(15)

(16) R = H
(17) R = Me

In conclusion, although the title reaction did not proceed according to the original aim, it presents a one step preparation of 3,3-disubstituted quinoline-2,4-diones [Equation (4)], including unusual modes of substitution, as demonstrated in the examples cited.

(4)

Experimental

M.p.s were taken with a Thomas-Hoover apparatus. I.r. spectra were recorded on a Perkin-Elmer 157 spectrometer (Nujol mulls) and n.m.r. spectra on a Bruker WH-200 spectrometer. Mass spectra (70 eV) were recorded on a Varian MAT-311 spectrometer. Light petroleum refers to the fraction with a boiling range of 40—60 °C.

N-*Tosyloxyphthalimide* (3).—The procedure of Cadogan[9] was followed, using triethylamine as the base. (The reported[9] use of diethylamine is probably an error.) The product was crystallized from ethanol, m.p. 161—162 °C.

Spiro[fluorene-9,3'-1',2',3',4'-*tetrahydroquinoline]*-2',4'-*dione* (9).—Butyl-lithium in hexane (10 mmol) was added to a cooled (−70 °C) solution of fluorene (1.66 g, 10 mmol) in dry tetrahydrofuran (20 ml). The mixture was stirred for 30 min under an argon atmosphere after which a solution of (3) (1.59 g,

5 mmol) in dry tetrahydrofuran was added to it. Stirring was continued until the temperature reached 15 °C (*ca.* 1.5 h) when the solution was poured into 0.1M-HCl (120 ml). The mixture was then extracted with dichloromethane (60 ml) and the extract dried (Na$_2$SO$_4$) and evaporated. The solid residue (2.3 g) was triturated twice with chloroform to give *compound* (9) (1.12 g, 75%), m.p. 312 °C (Found: C, 80.8; H, 4.3; N, 4.5. C$_{21}$H$_{13}$NO$_2$ requires C, 81.0; H, 4.2; N, 4.5%); ν$_{max.}$ 3 170 (NH), 1 690, and 1 650 cm^{-1} (C=O); *m/z* 311 (*M*$^+$, 100%), 192 (47), 163 (26), 155 (10), 146 (72), 119 (21), and 92 (10).

o-Fluorene-9-carboxamidobenzoic Acid (10).—(a) *Direct preparation*. The preparation of (9) described above was repeated, but the reaction mixture was poured into water instead of HCl. After extraction (CH$_2$Cl$_2$) and evaporation the residue was crystallized from chloroform–light petroleum and recrystallized from ethanol to give *compound* (10), m.p. 258—260 °C (0.95 g, 85%) (Found: C, 76.9; H, 4.6; N, 4.0. C$_{21}$H$_{15}$NO$_3$ requires C, 76.6; H, 4.6; N, 4.25%); ν$_{max.}$ 3 320 (NH), 1 685, and 1 670 cm^{-1} (C=O); *m/z* 329 (*M*$^+$, 23%), 311 (26), 192 (34), 166 (97), 165 (94), 164 (97), 146 (100), 119 (19), and 90 (25).

(b) *From compound* (9). The dione (9) (0.1 g) was stirred in 1M-NaOH (5 ml) for 15 min, during which time most of it dissolved. The insoluble material was filtered off and the filtrate acidified (2M-HCl). The precipitate was collected and crystallized from ethanol to give the carboxamide (10) (0.08 g, 80%).

2-*Fluoren*-9-*ylbenzo*[d][1,3]*oxazin*-4-*one* (11).—A solution of (10) (0.12 g) in acetic anhydride (5 ml) was refluxed for 1 h and poured into water (20 ml). The precipitated solid was filtered off and crystallized from chloroform–light petroleum to give *compound* (11) (0.1 g, 88%), m.p. 205 °C (Found: C, 80.7; H, 4.1; N, 4.4; C$_{21}$H$_{13}$NO$_2$ requires C, 81.0; H, 4.2; N, 4.5%); ν$_{max.}$ 1 740 and 1 630 cm^{-1} (C=O); δ(CDCl$_3$) 8.16 (1 H, dd, *J* 7.8 and 1.5 Hz), 7.8—7.25 (1 H, m), and 5.17 (1 H, s); *m/z* 311 (*M*$^+$, 22%), 192 (27), 166 (67), 165 (64), 164 (70), 146 (100), and 119 (18).

Spiro[indene-1,3'-1',2',3',4'-*tetrahydroquinoline]*-2',4'-*dione* (12).—The procedure described above for (9) was followed using indene (1.16 g, 10 mmol). The *product* (12) was obtained as light yellow crystals (0.82 g, 63%), m.p. 209 °C (Found: C, 78.5; H, 4.35; N, 5.1. C$_{17}$H$_{11}$NO$_2$ requires C, 78.15; H, 4.2; N, 5.4%); ν$_{max.}$ 3 180 (NH), 1 700, and 1 660 cm^{-1} (C=O); δ[SO(CD$_3$)$_2$] 7.1—7.7 (8 H, m), 7.06 (1 H, d), and 6.58 (1 H, d, *J* 5.7 Hz); *m/z* 261 (*M*$^+$, 100%), 233 (35), 204 (18), 146 (100), 142 (59), 119 (40), 114 (49), 92 (18), and 90 (18).

3-*Ethoxycarbonyl*-3-(2-*pyridyl*)*quinoline*-2,4-*dione* (13).—The reaction between ethyl 2-pyridylacetate (1.65 g, 10 mmol), butyl-lithium (10 mmol), and compound (3) (1.59 g, 5 mmol) was carried out as described above in the preparation of (9). The crude product was stirred with ether and the insoluble portion was filtered off and crystallized from chloroform–light petroleum to give *compound* (13) (0.25 g, 35%) as colourless cubes, m.p. 152 °C (Found: C, 65.7; H, 4.45; N, 8.9. C$_{17}$H$_{14}$N$_2$O$_4$ requires C, 65.8; H, 4.55; N, 9.0%); ν$_{max.}$ 3 200 (NH), 1 760, 1 710, and 1 670 cm^{-1} (C=O); δ(CDCl$_3$) 6.9—8.5 (9 H, m), 4.17 (2 H, q), and 1.15 (3 H, t); *m/z* 310 (*M*$^+$, 95%), 282 (55), 204 (71), 238 (100), 209 (97), 194 (91), 181 (44), 146 (95), 119 (44), 92 (59), 90 (42), and 78 (60).

Spiro[quinoline-3,2'-1',2',3',4'-*tetrahydronaphthalene]*-1',2,4-*trione* (14). A solution of di-isopropylamine (1.2 g, 12 mmol) in dry tetrahydrofuran (15 ml) was cooled to −70 °C, and BuLi (10 mmol, hexane solution) was added. The mixture was stirred in the cold for 30 min after which a solution of 1,2,3,4-tetrahydronaphthalen-1-one (1.46 g, 10 mmol) in dry tetrahydrofuran (15 ml) was added. Stirring was continued and after

30 min a solution of compound (3) (1.59 g, 5 mmol) in dry THF (20 ml) was added. When the temperature reached 15 °C the reaction mixture was poured into 0.2M-HCl (150 ml), and extracted with ether. After evaporation and removal of the excess 1,2,3,4-tetrahydronaphthalen-1-one under reduced pressure (0.1 mmHg, 100 °C) the residue was crystallized from ethanol to give *the trione* (14) (0.68 g, 47%) as light yellow crystals, m.p. 186 °C (Found: C, 74.4; H, 4.6; N, 4.7. $C_{18}H_{13}NO_3$ requires C, 74.2; H, 4.5; N, 4.8%); $v_{max.}$ 3 220 (NH), 1 690, and 1 640 cm^{-1} (C=O); δ(CDCl$_3$) 7.1—8.0 (8 H, m), 3.24 (2 H, m) and 2.8 (2 H, br d, *J* 17 Hz); *m/z* 291 (*M*$^+$, 100%), 273 (22), 263 (77), 246 (71), 234 (28), 186 (31), 118 (99), and 90 (87).

o-(2-Hydroxycyclohex-1-enecarboxamido)benzoic Acid (16).— The procedure as described above for (15), using cyclohexanone (0.98 g, 10 mmol) afforded, after distillation of the excess of cyclohexanone, a solid residue which was only partly soluble in chloroform. The insoluble fraction was triturated with chloroform to give the *carboxamide* (16) (0.45 g, 35%), m.p. 252—255 °C. The soluble fraction was treated, after evaporation, with 1M-NaOH solution, acidified, and filtered to give a further quantity of compound (16) (0.26 g, 20%) (Found: C, 64.5; H, 6.0; N, 5.4. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%); $v_{max.}$ 1 640 cm^{-1}; δ[SO(CD$_3$)$_2$] 7.4—8.4 (4 H, m), 3.0 (2 H, m), 2.66 (2 H, m), and 1.93 (4 H, br s); *m/z* 261 (*M*$^+$, 20%), 244 (17), 202 (56), 198 (16), 188 (48), 186 (23), 175 (100), 161 (14), and 130 (15).

Methyl o-(2-Methoxycyclohex-1-enecarboxamido)benzoate (17).—A solution of compound (16) (0.1 g) in methanol (10 ml) was treated with ethereal diazomethane (4 equiv.). The mixture was stirred at room temperature for 2 h and then evaporated to give an oily residue which was chromatographed on silica gel (5 g, chloroform as the eluant); this afforded a solid. Crystallization of the latter from chloroform–light petroleum gave the *ester* (17) (0.1 g) m.p. 72 °C (Found: C, 66.4; H, 6.5; N, 4.9. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.6; N, 4.8%); $v_{max.}$ 1 720 and 1 645 cm^{-1}; δ 7.3—8.2 (4 H, m), 3.97 (3 H, s), 3.66 (3 H, s), 2.63 (2 H, m), 2.43 (2 H, m), and 1.80 (4 H, br s). *m/z* 289 (*M*$^+$, 39%), 258 (34), 202 (68), 189 (100), 188 (45), and 174 (38).

Crystal Structure of Compound (9).—Crystals of (9), suitable for *X*-ray determination were obtained by slow crystallization from butanone. Crystallographic data: $C_{21}H_{13}NO_2$, M = 311.3, space group $P2_1/n$, a = 14.954(4), b = 8.814(2), c = 12.557(3) Å, β = 108.66(8)°, V = 1 568.1(5) Å^3, Z = 4. $F(000)$ = 648.00, D(calc.) = 1.32 g cm^{-3}, μ(Mo-K_α) = 0.48 cm^{-1}. Out of 2 028 unique reflections, 1 739 were with $I \geqslant 2\sigma(I)$.

Procedure. Data were measured on a PW1100/20 Philips four-circle computer controlled diffractometer. Mo-K_α (λ = 0.710 69 Å) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by a least-squares fit of 24 centred reflections in the range of $10 \leqslant \theta \leqslant 13°$. Intensity data were collected by using the ω-2θ technique to a maximum 2θ of 50°. The scan width, $\Delta\omega$, for each reflection was 1° with a scan time of 20 s. Background

measurements were made for other 20 s at both limits of each scan. Three standard reflections were monitored every 60 min. No systematic variations in intensities were found.

Intensities were corrected for Lorentz and polarization effects. All non-hydrogen atoms were found by using the results of the MULTAN direct method analysis.[10] After several cycles of refinements[11] the positions of the hydrogen atoms were calculated and added with a constant isotropic temperature factor of 0.5 Å^2 to the refinement process. Refinement proceeded to converge by minimizing the function $\Sigma\omega(|F_o| - |F_c|)^2$, where the weight, w, is $\sigma(|F_o|)^{-2}$. A final difference Fourier synthesis map showed several peaks less than 0.1 e Å^{-3} scattered about the unit cell without a significant feature.

The discrepancy indices, $R = \Sigma||F_o| - |F_c||\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2 z\Sigma w(|F_o|^2]1/2$, were 0.047 and 0.065 respectively. Full listings of the bond lengths and angles appear as a Supplementary Publication [Sup. No. 56364 (3 pp)].* The calculated and observed structure factors are available on request from the Editorial office.

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* For details of the Supplementary Publications scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans 1*, 1986, Issue 1.

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11 All crystallographic computing was done on a Cyber 74 computer at the Hebrew University of Jerusalem by using the SHELX 1977 structure-determination package.

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