A NEW SYNTHETIC ROUTE TO HETEROCYCLIC QUINONES

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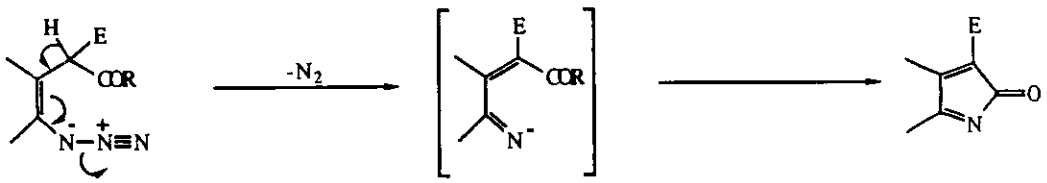
Abstract-The synthesis of a variety of heterocyclic quinones is described. This involves a series of unusual transformations of azidoquinones having an active methylene group in conjugation with the azide moiety. Generation of the conjugate base induces nitrogen loss and subsequent heterocyclic ring formation.

Reported here is a heterocyclic quinone synthesis which is formally outlined according to the generalized sequence represented in Scheme 1. Specifically, the transformations are viewed as arising from vinyl azides of structural type **1** (E = electron withdrawing group). Such compounds are induced to undergo elimination of dinitrogen to the imide ion intermediate **2** upon treatment with base. Subsequent intramolecular acyl transfer then results in the heterocyclic compounds **3**. Selected examples of such transformations starting with appropriately substituted azidoquinones are outlined below.

SCHEME 1

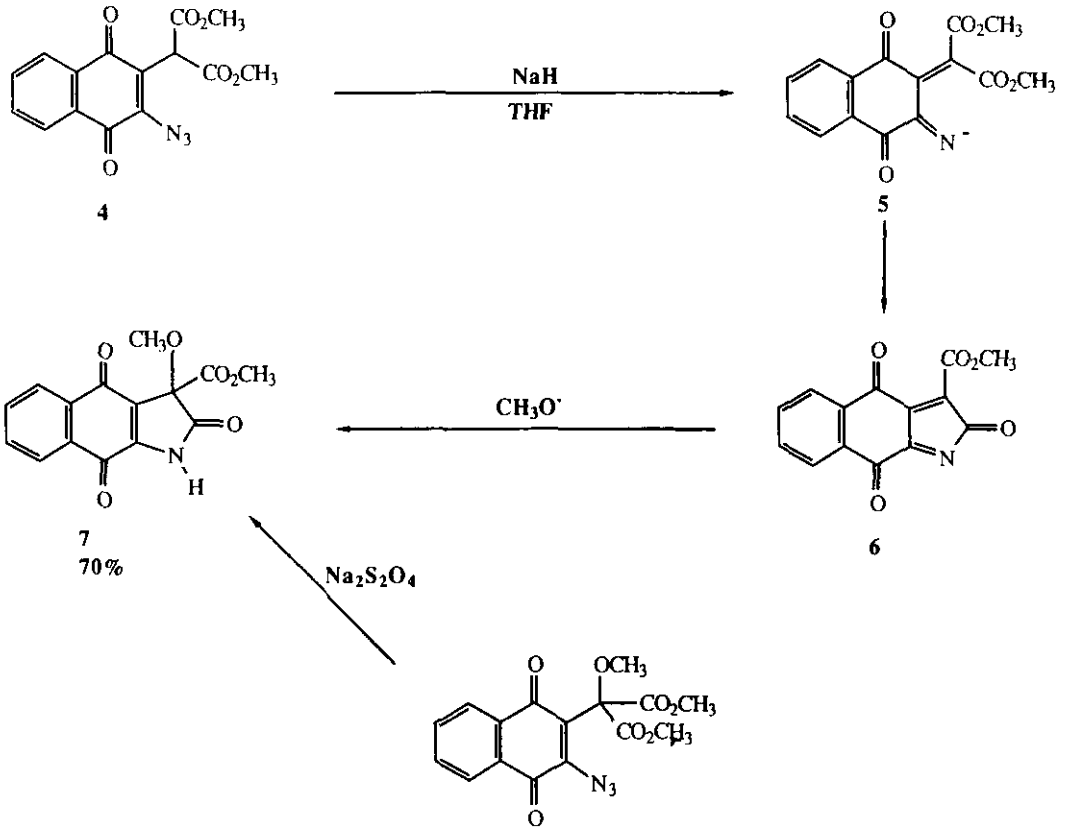


1 **2** **3**

Slow addition of a THF solution of the azidoquinone **4** to 1 eq. of NaH in THF resulted in the immediate evolution of N_2 (Scheme 2). After neutralization with HCl and standard isolation procedures the indolequinone **7** was obtained in 70% yield. The structure of **7** is based upon its spectral properties as well as its independent synthesis by treating the azidoquinone **8** with sodium dithionite.[1,2]

The conversion of **4** to **7** is envisaged to involve initial proton abstraction from the active methylene site. The resulting carbanion then promotes the elimination of dinitrogen to give the intermediate **5**. This then proceeds to the azadiene intermediate **6**. Subsequent Michael addition of the released methoxide ion to the electron deficient azadiene ultimately results in **7**.

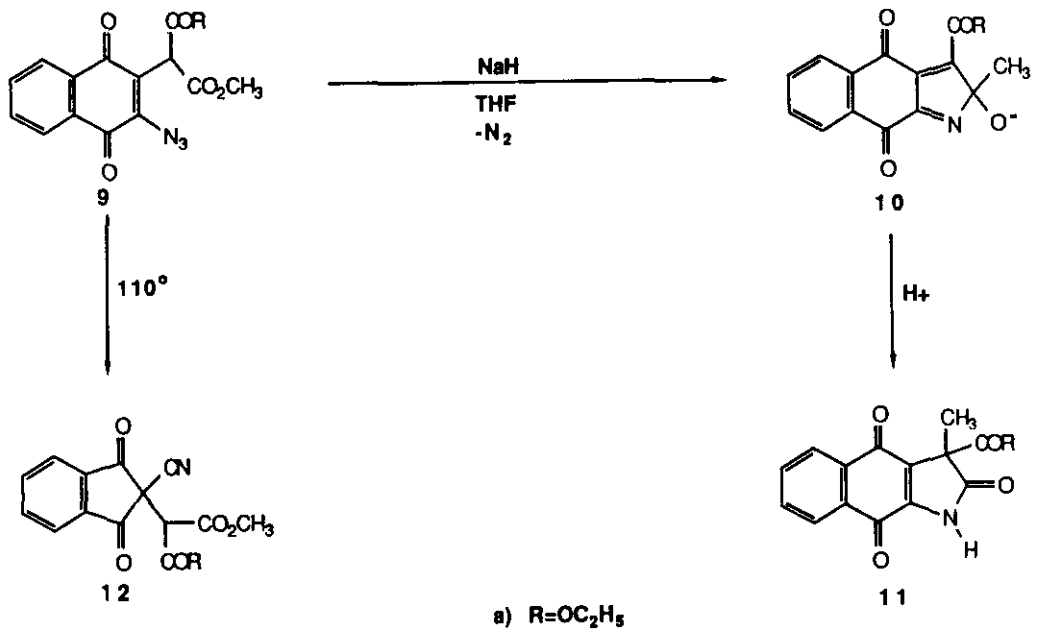
SCHEME 2



Interestingly, when the azidoquinone **9a** was subjected to the above conditions the reaction did not follow the same course (Scheme 3). Rather, the analogous proposed imidide ion intermediate apparently attracts the more electrophilic methyl ester moiety to give **10a**. This then undergoes an unusual oxo-assisted [1,5]-sigmatropic methyl shift to give **11a** (44%). Similar treatment of **9b** gives **11b** in 25% isolated yield.

It is interesting to compare the chemistry of **9** under the above basic condition to that observed upon thermolysis under neutral conditions. Here, rather than heterocyclic quinone formation, ring contraction to **12a,b** was observed when **9a,b** were subjected to thermal decomposition in refluxing toluene. Such a transformation is noteworthy but not unexpected on the basis of extensive studies which have previously appeared on the thermal rearrangements of azidoquinones.[3,4] In a further comparison study, the thermolysis of **13** was investigated (Scheme 4). Here, both **14** (35%) and **15** (40%) were realized. The former is viewed as arising via a mechanism similar to that suggested for the conversion of **9** to **11** except that nitrogen loss is facilitated by the nucleophilicity of an enol ether rather than a carbanion. The latter is again an example of the known thermal ring contraction of azidoquinones.[4]

SCHEME 3

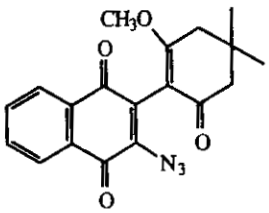


Finally it is noted that the indolequinone **17** was isolated in 47% yield when the azidoquinone **16** was slowly added to a THF suspension of sodium phenylthiolate (Scheme 5). Here again, an azadiene analogous to **6** is envisaged as the intermediate which gave the observed product after conjugated addition of the phenylthiolate ion. In comparison it is of interest to note that treatment of **16** with thiophenol rather than the thiolate anion results in displacement of the azide group rather than heterocyclic quinone formation.

EXPERIMENTAL

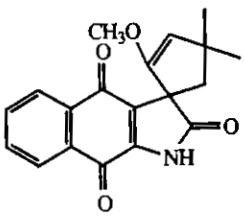
3-Carbomethoxy-3-methoxy-2,3,4,9-tetrahydrobenzo[f]indole-2,4,9-trione (7). A solution of azidoquinone **4** (0.500 g, 1.52 mmol) in 60 ml of THF was added dropwise to a stirred suspension of 50 mg of NaH (80% dispersion in oil, 1.66 mmol) in 100 ml of THF under N_2 atmosphere. The stirring was continued for 1 hour after the addition was completed, and then acidified with dilute HCl and extracted with CH_2Cl_2. The methylene chloride solution was dried ($MgSO_4$) and concentrated. Chromatography of the residue [ethyl acetate:hexane (3:7)] provided 7 (320 mg, 70%).[1]

SCHEME 4



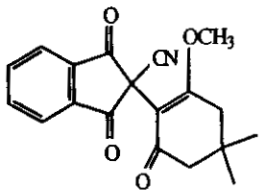
13

110°



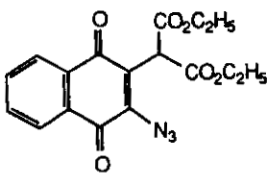
14
35%

+



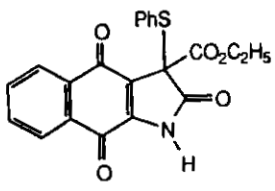
15
40%

SCHEME 5



16

PhSNa
THF



17
47%

3-Carboethoxy-3-methyl-2,3,4,9-tetrahydrobenzo[f]indole-2,4,9-trione (11a). A solution of azidoquinone **9a** (200 mg, 0.61 mmol) in 60 ml of dry THF was added dropwise to a stirred suspension of NaH (80% dispersion in oil, 20 mg, 0.61 mmol) in 100 ml of THF under N_2 atmosphere. The reaction solution was stirred for one half hour, and then acidified with dilute HCl and extracted with CH_2Cl_2. The methylene chloride solution was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue [ethyl acetate:hexane (5:5) as eluent) provided **11a** (80 mg, 44%) as a yellow solid: mp 207.5-208.5° (CH_2Cl_2-hexane); Ir (KBr, cm^{-1}) 3250 (m), 1715 (broad, s), 1640 (m), 1595 (m), 1550 (s); ^1H Nmr ($CDCl_3$) ∂ 1.29 (t, 3H, J=7 Hz), 1.86 (s, 3H), 4.26 (q, 2H, J=7 Hz), 7.70-7.91 (m, 2H), 8.08-8.29 (m, 2H); ^{13}C Nmr ($CDCl_3$) ∂ 14.17 (q), 20.85 (q), 63.27 (t), 72.70 (s), 108.12 (s), 126.96 (d), 127.67 (d), 131.93 (s), 132.99 (d), 134.72 (s), 136.43 (d), 165.13 (s), 166.10 (s), 177.14 (s), 179.60 (s), 192.04 (s); Ms m/e (relative intensity) 302 (M^+ -CO_2Et, 100%, EI). Exact mass Calcd for $C_{16}H_{13}NO_5$: 299.07935. Found: 299.08105.

3-Acetyl-3-methyl-2,3,4,9-tetrahydrobenzo[f]indole-2,4,9-trione (11b). To a stirred solution of NaH (80% dispersion in oil, 20 mg, 0.67 mmol) in 50 ml of THF was added dropwise a solution of azidoquinone **9b** (200 mg, 0.67 mmol) in 30 ml of THF. The reaction mixture was stirred for one half hour and the acidified with dilute HCl and extracted with CH_2Cl_2. The methylene chloride solution was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed (5:5 ethyl acetate:hexane) to give **11b** (45 mg, 25%) as a yellow solid: mp 187-189°; Ir (CH_2Cl_2, cm^{-1}) 3240 (w), 1700 (s), 1660 (s), 1640 (s), 1550 (m); ^1H Nmr ($CDCl_3$) ∂ 1.70 (s, 3H), 2.16 (s, 3H), 7.47-7.71 (m, 2H), 8.01-8.15 (m, 2H), 9.10 (broad, 1H); Ms m/e (relative intensity) 271 (M^+ +1, 40%, CI), 269 (M^+, 19%, EI). Exact mass Calcd for $C_{15}H_{11}NO_4$: 269.0688. Found: 269.0701.

2-Cyano-2-[(carboethoxy)(carbomethoxy)methyl]indan-1,3-dione (12a). A solution of azidoquinone **9a** (300 mg, 0.92 mmol) in 100 ml of dry toluene was heated under reflux for 2 hours. The solvent was removed after cooling, and the residue was chromatographed (ethyl acetate:hexane (3:7) as eluent) to give **12a** (195 mg, 71%) as a white solid which was recrystallized from CH_2Cl_2-hexane: mp 129-130°; Ir (KBr, cm^{-1}) 3440 (w), 1730 (s), 1720 (s), 1600 (m); ^1H Nmr ($CDCl_3$) ∂ 0.85 (t, 3H, J=7 Hz), 2.49 (s, 3H), 3.94 (q, 2H, J=7 Hz), 7.90 (braod, 1H), 7.88-7.98 (m, 2H), 8.05-8.14 (m, 2H); Ms m/e (relative intensity) 299 (M^+, 23%, EI), 253 (M^+ - C_2H_5OH, 73%), 226 (M^+ -CO_2Et, 78%). Exact mass Calcd for $C_{16}H_{13}NO_5$: 299.0794. Found: 299.0801.

2-Cyano-2-[(acetyl)(carbomethoxy)methyl]indan-1,3-dione(12b). The title compound was obtained in 64% as white crystals: mp 132-133; Ir (KBr, cm^{-1}) 3260 (s), 1775 (w), 1760 (m), 1725 (s), 1715 (s), 1690 (s), 1630 (s); ^1H Nmr ($CDCl_3$) ∂ 2.33 (s, 3H), 2.53 (s, 3H), 7.70 (broad, 1H), 7.87-7.91 (m, 2H), 8.05-8.13 (m, 2H); Ms m/e (relative intensity) 270 (M^+ + 1, 100%, CI), 269 (M^+, 67%, EI), 227 (100%, EI). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12. Found: C, 66.73; H, 4.02.

2,3,4,9-Tetrahydrobenzo[f]indole-2,4,9-trione-3-spiro-3-(2'-methoxy-4',4'-dimethylcyclopentene) (14) and 5,5-Dimethyl-3-methoxy-2-(2-cyano-1,3-dioxo-2-indanyl)-2-cyclohexene-1-one (15). A solution of azidoquinone **13** (600 mg, 1.71 mmol) in 100 ml of dry toluene was heated under reflux for 4 hours. The solvent was removed after cooling and the residue was chromatographed with ethyl acetate:hexane (5:5) as eluent, to give **14** (195 mg, 35%) and **15** (220 mg, 40%). **Compound 14:** White solid (CH_2Cl_2/hexane), mp 195-196°: Ir (Nujol, cm^{-1}) 3320 (w), 1775 (m), 1750 (m), 1730 (s), 1650 (s), 1610 (s); ^1H Nmr ($CDCl_3$) ∂ 1.14 (s, 6H), 2.18 (s, 2H), 2.62 (s, 2H), 3.99 (s, 3H), 7.87-7.93 (m, 2H), 8.01-8.06 (m, 2H); Ms m/e (relative intensity) 323 (M^+, 82%, EI), 279 (78%), 264 (100%). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30. Found: ; C, 70.83; H, 5.27. **Compound 15:** Yellow solid (ethyl acetate) mp 288-289°; Ir (KBr, cm^{-1}) 3200 (w), 1737 (s), 1680 (s), 1660 (s), 1626 (m), 1697 (m); ^1H Nmr ($CDCl_3$) ∂ 1.36 (s, 3H), 1.40 (s, 3H), 2.14 (d, 1H, J=13.3 Hz), 2.40 (d, 1H, J=13.3 Hz), 3.53 (s, 3H), 4.83 (s, 1H), 7.60 (broad, 1H), 7.66-7.80 (m, 2H), 8.06-8.12 (m, 2H); Ms m/e (relative intensity) 324 (M^+ +1, 90%, CI), 326 (M^+ +3, hydroquinone, 100%, CI), 323 (M^+, 10%, EI), 308 (M^+ -CH_3, 100%, EI) Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30. Found: 70.58, H, 5.30.

3-Carboethoxy-3-thiophenyl-2,3,4,9-tetrahydrobenzo[f]indole-2,4,9-trione (17). To a stirred solution of thiophenol (155 mg, 1.41 mmol) and NaH (80% dispersion in oil), 42 mg, 1.41 mmol) in 50 ml of dry THF was added dropwise a solution of azidoquinone **16** (0.50 g, 1.40 mmol) in 30 ml of THF. The reaction solution was stirred for one half hour after the addition was complete, and then acidified with dilute HCl and extracted with CH_2Cl_2. The methylene chloride solution was washed with water, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue (ethyl acetate:hexane (5:5) with 1% formic acid as eluent) provided **17** (260 mg, 47%) as a purple solid: mp 183-185°; ^1H Nmr ($CDCl_3$) ∂ 1.40 (t, 3H, J=7 Hz), 4.49 (q, 2H, J=7 Hz), 7.34-7.75 (m, 7H), 8.01-8.09 (m, 1H), 8.15-8.23 (m, 1H), 11.90 (s, 1H); Ir (KBr, cm^{-1}) 3200 (broad, m) 1740 (s), 1670 (s), 1600 (s); Ms m/e (relative intensity) 393 (M^+, 20%, EI). Exact mass Calcd for $C_{21}H_{15}NSO_5$: 393.0671. Found: 393.0654.

ACKNOWLEDGEMENT

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REFERENCES

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2. Dithionite reduction of azidoquinones results in azidohydroquinones which disproportionate to aminoquinones. See: Moore, H. W.; Shelden, H. R.; Shellhamer, D. F., *J. Org. Chem.*, **1968**, *33*, 1999.
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4. Moore, H. W., *Chem. Soc. Rev.*, **1973**, *2*, 415.

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