Synthesis of Polycyano-Substituted Azulenes via Direct Oxidative Cyanation Reaction

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Abstract: The synthesis of dicyano-, tricyano-, and tetracyanoazulenes substituted on both rings via direct oxidative cyanation reaction is described. 1-Cyanoazulene or 1,3-dicyanoazulene treated with tetraethylammonium cyanide (Et₄N⁺CN⁻) and subsequently with DDQ or para-chloranil were transformed stepwise into the desired polycyano-substituted azulenes.

Key words: arenes, cyanoazulenes, cyanation, nucleophilic addition, oxidative substitution.

Aromatic compounds bearing electron-withdrawing substituents, e.g. trinitrobenzene, para-tetracyanoquinodimethane, etc., are able to form charge-transfer complexes with electron rich partners.1 These complexes exhibit interesting physical properties behaving as semiconductors, organic metals, etc.2 To the category of strongly electron-deficient arenes, able to form such complexes also belongs 2,4,6,8-tetracyanoazulene (TCNA). Synthesis of this interesting molecule and its properties as an electron acceptor was recently reported by Hafner.3

In our studies on nucleophilic substitution of hydrogen in electron-deficient arenes via vicarious nucleophilic substitution (VNS)4 and oxidative nucleophilic substitution of hydrogen (ONSH)5 we have found that anionic σ⁺-adducts of carbanions and some other nucleophiles to azulene derivatives can be directly converted into corresponding substituted products via VNS and ONSH pathways.6 Since earlier reports on 2,4,6,8-TCNA revealed its many interesting properties3 we have attempted to elaborate the synthesis of other polycyanoazulenes using an approach developed in our laboratory – direct oxidation of anionic σ⁺-adducts of CN⁻ anion to substituted azulenes. For the cyanation reaction we have used tetraethylammonium cyanide (Et₄N⁺CN⁻, TEAC; Fluka) readily soluble in dichloromethane, chloroform, and other moderately polar, low boiling solvents.

The attempts at direct cyanation of unsubstituted azulene (1) (4 equiv of TEAC, in DMF, r.t.; then oxidation with DDQ at –78°C) did not give the desired cyano-compound; the only isolated product 2, was apparently formed via substitution of the CN group in DDQ by the azulene moiety (Scheme 1). Absence of the cyanation product is in agreement with the observation reported by Hafner et al.3 that azulene was insufficiently active as an electrophilic partner for the reaction with such a weak nucleophile as CN⁻ anion.

Scheme 1

Scheme 2
To complement polycyanoazulenes prepared by Hafner, we have chosen for further studies 1-cyanoazulene (3) and 1,3-dicyanoazulene (4), both readily prepared via Vilsmeier mono- and di-formylation of azulene, followed by standard conversion of the 1-formyl and 1,3-diformyl-azulenes produced into their respective cyanoazulenes. Treatment of 1-cyanoazulene (3) with an excess of sodium cyanide in liquid ammonia (−33 °C), followed by oxidation with potassium permanganate, did not result in oxidative cyanation and mainly the starting 3 was recovered from the reaction mixture (88%). On the other hand, the reaction of 1-cyanoazulene (3) with TEAC, in dichloromethane at various temperatures, resulted in partial conversion of 3 into the σH-adducts as is indicated by the change in coloration of the mixture. Formation of the corresponding σH-adducts by addition of CN− to 3 (three regioisomers, 5a, 6a, and 7a) was also evidenced via 1H NMR spectroscopic analysis of the homogeneous reaction mixture in THF-d8 – on the basis of the observed diagnostic signals at ca. 5 ppm originating from CH-sp3 protons (Scheme 2).

The best preparative results were obtained when the reaction was carried out at 0–5 °C with TEAC (2 equiv) and oxidation of such mixture with DDQ (2 equiv). Under these conditions we observed the formation of the three possible isomeric cyanation products: 1,4-dicyano- (5, 13%), 1,8-dicyano- (6, 8%), and 1,6-dicyano-azulene (7, 0.4%); with the overall yield of the cyanation being rather low (22%). These dicyanoazulenes were accompanied with small amounts of 1,4,8-tricyanoazulene (8; 3%), apparently formed via further oxidative cyanation of 5 or 6. The yields of the major products (5 and 6) were improved to 20% and 13% respectively when oxygen was bubbled through the reaction mixture at this temperature over ca. 2.5 h, and then, the mixture was quenched with DDQ.

The same reaction carried out at −60 °C resulted in recovery of the substrate 3 (97%). This result is in agreement with the absence of the cyanation reaction in liquid ammonia at −33 °C; however, it is not clear whether the negative result was due to a low degree of conversion of 3 into the corresponding σH-adducts 5a–7a at this temperature or the failure of oxidation of the σH-adducts – due to solubility problems.

On the other hand, addition of CN− to the more electrophilic 1,3-dicyanoazulene (4) in chloroform, at room temperature, led to the completion of the reaction as indicated by the disappearance of the characteristic color of the azulene derivative and also by the 1H NMR spectrum of the reaction mixture. Oxidation of the mixture with para-chloranil (3 equiv) gave a mixture of 1,3,4- and 1,3,6-tricyanoazulenes 9 and 10 in high overall yield (85%) (Scheme 3). The same reaction carried out in chloroform at low temperature (−78 °C → −10 °C), followed by oxidation with DDQ (at −60 °C), led to both isomers 9 and 10 being obtained in excellent yield (91% and 4% respectively).

The resulting tricyanoazulenes 9 and 10 were subjected to further cyanation with TEAC in dichloromethane. Again the addition of CN− anion proceeded rapidly as indicated by the discoloration of the mixture, however the σH-adducts formed were resistant to oxidation with para-chloranil. The σH-adduct formed, 11a, was also relatively unstable at room temperature (1H NMR examination in CDCl3); thus, at this temperature tars were formed, whereas at −57 °C considerable amounts of the starting material were recovered. On the other hand, oxidation of the adduct 11a proceeded satisfactorily with DDQ (2 equiv), in dichloromethane at low temperature (−78 °C), to give the desired 1,3,4,8-tetracyanoazulene (11). This result might be simply explained by a relatively low oxidative poten-
tial of para-chloranil (E_{1/2} = +0.01 V)\(^8\) – probably insufficient for oxidation of the anionic σ\(^H\)-adduct 11a, effectively stabilized by four cyano groups. Oxidation at low temperature in dichloromethane with DDQ, possessing higher oxidative potential (E_{1/2} = +0.51 V),\(^3\) proceeded efficiently to give the expected product 11. This product was obtained and isolated in excellent yield (94%), however it was rather unstable, so all the operations should be executed rapidly; flash filtration throughout silica gel provides analytically pure material for full characterization and the product should be stored in refrigerator.

Cyanation of azulene-1,3,6-tricarbonitrile (10) under the same reaction conditions gave 1,3,4,6-tetracyanoazulene in high yield (12, 89%). Similarly to compound 11, it was also rather unstable.

Thus, starting from readily available 1,3-dicyanoazulene (4) in a simple two step operation 1,3,4,8- and 1,3,4,6-tetracyano-azulenes (11 and 12) were obtained in excellent overall yields (ca 90%). Attempts to convert 11 and 12 into 1,3,4,6,8-pentacyano-azulene, in the reactions with TEAC and DDQ or Et\(_4\)N\(^+\)MnO\(_4\) as oxidants, were unsuccessful. It appears that the corresponding σ\(^H\)-adducts formed are unstable and resistant to oxidation with these oxidants. It is also known that oxidation of σ\(^H\)-adducts of naphthoquinone to more electron-deficient arenes is a difficult process.\(^9\)

Cyanation of 1-Cyanoazulene

Procedure A

To a stirred solution of 3 (714 mg, 4.7 mmol) in CH\(_2\)Cl\(_2\) (100 mL), cooled to 5 °C, was added TEAC (1.458 g, 9.3 mmol) dissolved in CH\(_2\)Cl\(_2\) (5 mL). After 2.5 h a suspension of DDQ (2.118 g, 9.3 mmol) in CH\(_2\)Cl\(_2\) (7 mL) was added at 5 °C. After 1 h of stirring at this temperature the reaction mixture was filtered through a thin layer of silica gel, the solvent was removed in vacuo and the residue was chromatographed on silica gel to give recovered 3 (hexane–CHCl\(_3\), 1:1; 163 mg, 23%), and then the products 5–8 (hexane–CH\(_2\)Cl\(_2\), 1:2).

Procedure B

The reaction was carried out as in procedure A; during the reaction time oxygen was passed throughout the reaction mixture. Compound 3 was recovered in 3% yield.

1,4-Dicyanoazulene (5)

Yield: 13% (Procedure A), 20% (Procedure B); green solid (dark-blue in solution of CHCl\(_3\)); mp 211–213 °C.

1H NMR (400 MHz, acetone–d\(_6\)) \(\delta = 8.87\) (d, 1 H, J = 9.5 Hz, H-5), 8.77 (d, 1 H, J = 9.5 Hz, H-8), 8.44 (d, 1 H, J = 4.2 Hz, H-2), 8.01 (d, 1 H, J = 9.5 Hz, H-7), 7.72 (d, 1 H, J = 4.2 Hz, H-3).

HRMS (EI): \(m/z =\) 178 (100, M\(^+\)), 151 (32, M – HCN), 129 (45), 124 (5, M – 2 × HCN).

HRMS (EI): \(m/z =\) Calculated for C\(_{12}\)H\(_8\)N\(_2\), 178.0531; found, 178.0524.


Found: C, 60.80; H, 3.41; N, 15.63.

1,6-Dicyanoazulene (7)

Yield: 0.4% (Procedure A), 1% (Procedure B); green solid (dark-blue in solution of CHCl\(_3\)); mp 232–234 °C.

1H NMR (400 MHz, acetone–d\(_6\)) \(\delta = 8.82\) (d, 1 H, J = 9.5 Hz, H-5), 8.77 (d, 1 H, J = 9.5 Hz, H-8), 8.44 (d, 1 H, J = 4.2 Hz, H-2), 8.01 (d, 1 H, J = 9.5 Hz, H-7), 7.72 (d, 1 H, J = 4.2 Hz, H-3).

HRMS (EI): \(m/z =\) 178 (100, M\(^+\)), 151 (32, M – HCN), 129 (45), 124 (5, M – 2 × HCN).

HRMS (EI): \(m/z =\) Calculated for C\(_{12}\)H\(_8\)N\(_2\), 178.0531; found, 178.0524.

1,8-Dicyanoazulene (6)

Yield: 8% (Procedure A), 13% (Procedure B); green solid (dark-blue in solution of CHCl\(_3\)); mp 238–239 °C.

1H NMR (400 MHz, acetone–d\(_6\)) \(\delta = 8.91\) (d, 1 H, J = 8.5 Hz, H-4), 8.40 (d, 1 H, J = 4.3 Hz, H-2), 8.15 (apparent t, 1 H, J = ca. 9.0 Hz, H-6), 7.99-7.89 (m, 2 H, H-5, H-7), 7.71 (d, 1 H, J = 4.3 Hz, H-3).

HRMS (EI): \(m/z =\) 178 (100, M\(^+\)), 151 (23, M – HCN), 127 (8), 124 (6, M – 2 × HCN).

HRMS (EI): \(m/z =\) Calculated for C\(_{12}\)H\(_8\)N\(_2\), 178.0531; found, 178.0534.


Found: C, 80.79; H, 3.15; N, 15.68.

1,4,8-Tricyanoazulene (8)

Yield: 3% (Procedure A), 0.4% (Procedure B); light-green solid (blue in solution of CHCl\(_3\)); mp 240–241 °C.

1H NMR (400 MHz, acetone–d\(_6\)) \(\delta = 8.77\) (d, 1 H, J = 4.3 Hz, H-2), 8.33 (dd, 1 H, J = 11.6, 8.3 Hz, H-6), 8.22 (m, 1.4 Hz, H-5, J = 4.3 Hz, H-3).

HRMS (EI): \(m/z =\) 178 (100, M\(^+\)), 151 (23, M – HCN), 127 (8), 124 (6, M – 2 × HCN).

HRMS (EI): \(m/z =\) Calculated for C\(_{12}\)H\(_8\)N\(_2\), 178.0531; found, 178.0534.


Found: C, 80.79; H, 3.15; N, 15.68.

1,8-Tricyanoazulene (8)

Yield: 3% (Procedure A), 0.4% (Procedure B); light-green solid (blue in solution of CHCl\(_3\)); mp 240–241 °C.

1H NMR (400 MHz, acetone–d\(_6\)) \(\delta = 8.77\) (d, 1 H, J = 4.3 Hz, H-2), 8.33 (dd, 1 H, J = 11.6, 8.3 Hz, H-6), 8.22 (m, 1.4 Hz, H-5, J = 4.3 Hz, H-3).

HRMS (EI): \(m/z =\) 178 (100, M\(^+\)), 151 (23, M – HCN), 127 (8), 124 (6, M – 2 × HCN).

HRMS (EI): \(m/z =\) Calculated for C\(_{12}\)H\(_8\)N\(_2\), 178.0531; found, 178.0534.


Found: C, 80.79; H, 3.15; N, 15.68.
MS (EI): m/z (%): 203 (100, M⁺), 178 (78), 176 (39, M – HCN), 152 (31), 151 (35, M – 2 × CN), 125 (13), 124 (14, M – 3 × CN).

HRMS (EI): m/z calculated for C₁₃H₅N₃: 203.0483; found: 203.0498.


Cyanation of 1,3-dicyanoazulene

Procedure A

To a stirred solution of 4 (100 mg, 0.562 mmol) in CHCl₃ (50 mL) at ambient temperature was added TEAC (114 mg, 0.73 mmol) dissolved in CHCl₃ (5 mL). After 2 h p-chloranil (400 mg, 1.627 mmol) was added in one portion. The reaction was continued for 18 h. Then, the solvent was removed in vacuo and the residue was chromatographed on silica gel (hexane–CHCl₃, 1:1) to give products 9 (80%) and 10 (5%).

Procedure B

To a stirred solution of 4 (24 mg, 0.135 mmol) in CHCl₃ (30 mL), cooled to –10 °C, was added TEAC (42 mg, 0.269 mmol) dissolved in CHCl₃ (3 mL). After 5 h of stirring at this temperature the reaction mixture was cooled to –60 °C and then a suspension of DDQ (35 mg, 0.154 mmol) in CH₂Cl₂ (2 mL) was added. After 0.5 h the cold reaction mixture (–78 °C) was rapidly chromatographed through a small column (CHCl₃), then the solvent was removed in vacuo at r.t. to give 12.

Yield: 90%; green solid (blue in a solution of CHCl₃); unstable, decomposition ca. 265–280 °C.

1H NMR (200 MHz, CDCl₃): δ = 7.09 (d, 1 H, J = 10.5 Hz, H-8), 6.88 (s, 1 H, H-2), 6.29–6.11 (m, 2 H, H-5, H-7), 5.51 (apparent t, 1 H, J = ca. 9.0 Hz, H-6), 4.91 (d, 1 H, J = 8.6 Hz, H-4).

10 (minor isomer, 5%)

1H NMR (200 MHz, CDCl₃, diagnostic signals): δ = 6.94 (d, 2 H, J = ca. 9.2 Hz, H-4, H-8), 5.20 (dd, 2 H, J = ca. 9.2, 7.2 Hz, H-5, H-7).

Counterion Et₄N⁺: 3.30 (q, 2 H, J = ca. 7.3 Hz, CH₃).

Adducts 9a, 10a

Mixture of 4 with TEAC at r.t.

9a (major isomer, 95%)

1H NMR (200 MHz, CDCl₃): δ = 7.09 (d, 1 H, J = 10.5 Hz, H-8), 6.88 (s, 1 H, H-2), 6.29–6.11 (m, 2 H, H-5, H-7), 5.51 (apparent t, 1 H, J = ca. 9.0 Hz, H-6), 4.91 (d, 1 H, J = 8.6 Hz, H-4).

10a (minor isomer, 5%)

1H NMR (200 MHz, CDCl₃): δ = 6.94 (d, 2 H, J = ca. 9.2 Hz, H-4, H-8), 5.20 (dd, 2 H, J = ca. 9.2, 7.2 Hz, H-5, H-7).

Counterion Et₄N⁺: 3.30 (q, 2 H, J = 7.3 Hz, CH₃).

Adduct 11a

Mixture of 9 with TEAC, at r.t.

1H NMR (200 MHz, CDCl₃): δ = 7.01 (s, 1 H, H-2), 6.84 (d, 1 H, J = 6.4 Hz, H-7), 6.29 (dd, 1 H, J = ca. 10.0, 6.4 Hz, H-6), 5.86 (dd, 1 H, J = ca. 10.0, 8.5 Hz, H-5), 4.94 (d, 1 H, J = 8.5 Hz, H-4).

Counterion Et₄N⁺: 3.30 (q, 2 H, J = 7.3 Hz, CH₃), 1.36 (t, 3 H, J = 7.3 Hz, CH₃).

References