Thermolysis of 2-(3-phenylsulfonylprop-1-ynyl)benzonitrile: an aza-Myers type cyclization to isoquinolines

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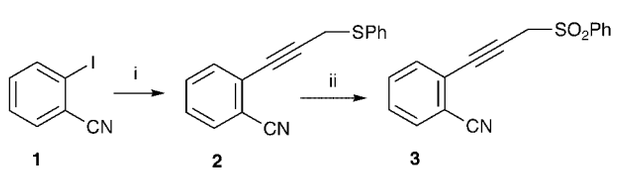
Thermolysis of 2-(3-phenylsulfonylprop-1-ynyl)benzonitrile (3) in refluxing benzene containing cyclohexa-1,4-diene and triethylamine gave isoquinolone 4 in 7% yield and compound 5 in 10% yield and 14% of the starting material was recovered. When this cyclization reaction was carried out under oxygen atmosphere, compound 4 was isolated in 14% yield and 20% of the starting benzonitrile 3 was recovered. Under refluxing carbon tetrachloride, cyclization of 3 gave the chloroisoquinoline 6 in 18% yield and 5 in 22% yield. The isolation of compounds 4 and 6 strongly suggests the formation of biradical 8 through a (*Z*)-hexa-2,4,5-trienenitrile intermediate 7.

The mechanism of the formation of biradicals derived from enediyne antitumor antibiotics has attracted much attention due to their DNA-cleaving properties.[1] In 1972, Jones and Bergman reported the thermal cyclization of (*Z*)-hex-3-ene-1,5-diynes to 1,4-didehydrobenzene diradicals.[2] This cyclization is considered to be the major mode of formation of biradical intermediates in enediyne antitumor antibiotics. In studies on the mechanism of the DNA-cleaving activity of the neocarzinostatin chromophore, Myers and co-workers reported the cyclization of (*Z*)-hepta-1,2,4-trien-6-ynes to α,3-didehydrotoluene.[3] Several potent DNA-cleaving agents have been developed based on Myers cyclization.[4,5] A similar cyclization occurs in the thermolysis of alkynylcyclobuten-4-one in which a biradical containing aryl and phenoxyl radical centers is produced *via* an enyne-ketene, as described by Moore and Yerxa.[6] An alternative pathway to enyne-ketenes was reported by Saito and co-workers, which involved the photochemical Wolff rearrangement of enynyl α-diazo ketones.[7] Recently, efforts have been made to cycloaromatize a conjugated system involving heteroatoms.[8] Among these studies, there are two reports that describe the cyclization of (*Z*)-hexa-2,4,5-trienenitrile systems. One failed to obtain the cyclization product and the other obtained aniline adducts through an unusual stabilized allylic radical addition to nitrile.[9] In this communication, we report the first successful example to isolate isoquinoline derivatives by thermolysis of 2-(3-phenylsulfonylprop-1-ynyl)benzonitrile (**3**) under alkaline conditions.

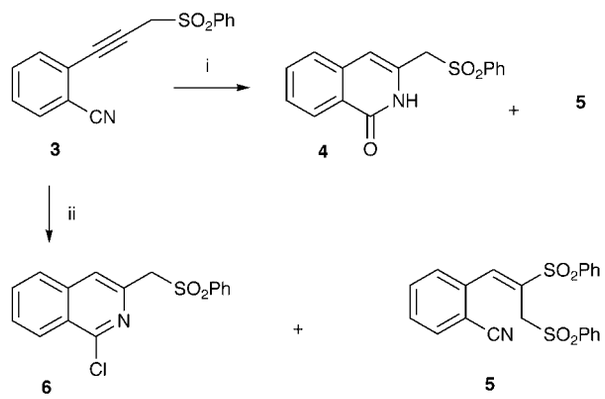
The synthesis 2-(3-phenylsulfonylprop-1-ynyl)benzonitrile (**3**) is outlined in Scheme 1. 2-Iodobenzonitrile (**1**) was directly



Scheme 1 *Reagents and conditions*: i) $HC{\equiv}CCH_2SPh$, $Pd(PPh_3)_4$, Et_2O, CuI, $BuNH_2$, 46%; ii) MCPBA, CH_2Cl_2, 76%.

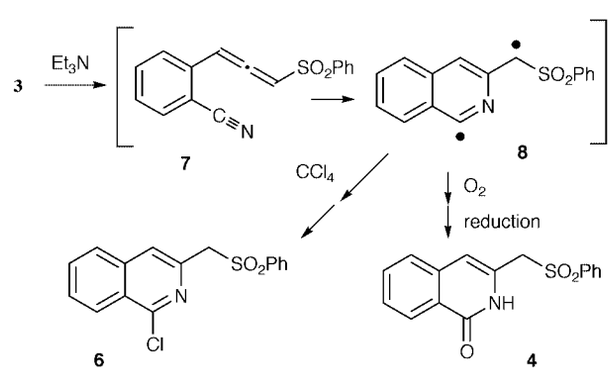
coupled to propargyl phenyl sulfide using tetrakis(triphenylphosphine)palladium(0) as the catalyst in the presence of cuprous iodode and *n*-butylamine, to give 2-(3-phenylthioprop-1-ynyl)benzonitrile (**2**) in 46% yield. Oxidation of sulfide **2** with 3 equivalents of MCPBA gave compound **3** in 76% yield.

When a benzene solution of **3** (0.01 M), containing cyclohexa-1,4-diene (1.5 M) and Et_3N (3 equiv.), was heated to reflux for 2.5 days, isoquinolone **4** was obtained in 7% yield and compound **5** was produced in 10% yield after preparative-scale thin layer chromatography. 14% of the starting nitrile **3** is recovered (Scheme 2).[10] When compound **3** was stirred in refluxing carbon



Scheme 2 *Reagents and conditions*: i cyclohexa-1,4-diene, benzene, Et_3N, reflux, 2.5 days, **4** (7%) and **5** (10%). ii) CCl_4, reflux, 2 days, **6** (18%) and **5** (20%).

tetrachloride in the presence of Et_3N for two days, the 1-chloroisoquinoline **6** was isolated in 18% yield along with compound **5** in 22% yield. The structure of compound **5** was unambiguously determined by X-ray crystallography. The isolation of compounds **4** and **6** strongly suggests the biradical intermediate **8** is the intermediate of this cyclization reaction. A rational explanation for the formation of compounds **4** and **6** is proposed (Scheme 3). Base-catalyzed isomerization of



Scheme 3

propargyl sulfone **3** gives allenyl sulfone **7** which is not isolable and subsequently undergoes a Myers-type cyclization to produce the biradical intermediate **8**. Trapping the σ-radical of **8** with molecular oxygen and the α-radical with cyclohexadiene gives compound **4**. On the other hand, trapping the σ-radical

of **8** with carbon tetrachloride and hydrogen abstraction by the α-radical possibly from triethylamine leads to **6**. In order to examine our hypothesis for the formation of compound **4**, a control experiment was carried out; treatment of **3** with Et_3N under refluxing benzene and cyclohexa-1,4-diene under oxygen atmosphere for 24 h. Compound **4** was isolated in 14% yield and 20% of the starting nitrile **3** was recovered. The increased amount of compound **4** isolated under these conditions supports our hypothesis. The mechanism for the formation of compound **5** is not clear at this stage. A possible pathway is proposed. In the base-catalyzed isomerization of propargyl sulfone to allenyl sulfone, a small amount of phenyl sulfonyl anion was produced *via* an E_i mechanism. The phenyl sulfonyl anion then added to the allenyl sulfone **7** *via* a 1,4-addition to give compound **5**.

In conclusion, we have demonstrated the first successful example of thermal cyclization of the (*Z*)-hexa-2,4,5-trienenitrile system to form isoquinoline derivatives and proved that this cyclization involved a diradical intermediate. The discovery of this new method of biradical formation provides a valuable source for theoretical study of enediyne related systems and an opportunity to design new DNA-cleaving antitumor agents.

Acknowledgements

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Notes and references

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10 Some physical properties of **2**, **3**, **5**, **6** and **7**. **2**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19–7.64 (m, 9H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 49.9 MHz) δ 134.8, 132.7, 132.6, 132.2, 130.5, 129.1, 128.3, 127.1, 126.8, 125.3, 117.4, 115.3, 92.4, 79.7, 60.4; MS (EI) *m*/*z* 249 (M^+, 100%), 140 (85%) (HRMS (EI) calcd. for $C_{16}H_{11}NS$ 249.0613. Found 249.0609). **3**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.07 (dd, 2H, J = 8.4, 1.4 Hz), 7.44–7.72 (m, 7H), 4.29 (s, 2H); ^{13}C NMR ($CDCl_3$, 49.9 MHz) δ 137.8, 134.4, 133.0, 132.8, 132.4, 129.3, 129.2, 128.8, 125.4, 117.0, 115.3, 83.5, 83.4, 49.3; MS (EI) *m*/*z* 281 (M^+, 5%), 233 (7%), 140 (100%) (HRMS (EI) calcd. for $C_{16}H_{11}NO_2S$ 281.0511. Found 281.0516). **4**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, 2H, J = 8.1 Hz), 7.51–7.69 (m, 6H), 7.35 (t, 1H, J = 7.6 Hz), 6.21 (s, 1H), 4.27 (s, 2H); MS (EI) *m*/*z* 299 (M^+, 23%), 267 (36%), 158 (100%) (HRMS calcd. for $C_{16}H_{13}NO_3S$ 299.0617. Found 299.0608). **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (s, 1H), 7.93 (dd, 2H, J = 8.6, 1.1 Hz), 7.46–7.76 (m, 14H), 4.42 (s, 2H); MS (EI) *m*/*z*, 282 ($M^+ - C_6H_5SO_2$), 218 (17), 141 (38), 77 (100) (HRMS calcd. for $C_{16}H_{12}NOS$ ($M^+ - C_6H_5SO_2$) 282.0590. Found 282.0590). **6**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (dt, 1H, J = 7.9, 0.7 Hz), 7.86 (dt, 2H, J = 7.9, 0.7 Hz), 7.42–7.73 (m, 6H), 6.64 (s, 1H), 4.26 (d, 2H, J = 3.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.9, 138.3, 136.1, 135.1, 134.5, 129.7, 129.4, 129.2, 128.5, 128.4, 126.0, 120.7, 109.5, 29.7 (HRMS calcd. for $C_{16}H_{12}O_2N^{35}ClS$ 317.0279. Found 317.0266).

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