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FORMATION AND PHOTOCHEMICAL ISOMERIZATION OF ARYLATED 1,3-DIHYDRO-2H-AZEPIN-2-ONES

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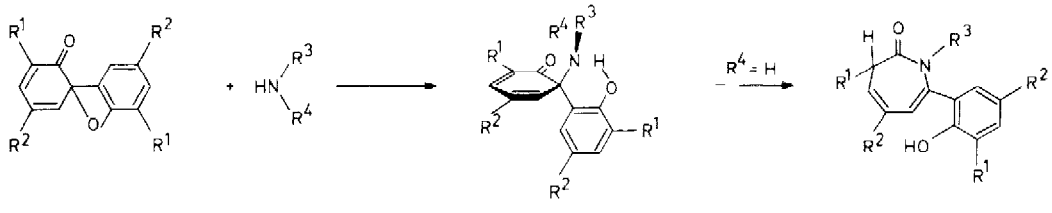
We have found a remarkably simple one-step synthesis of arylated 1,3-dihydro-2H-azepinones (5) from spiroquinol ethers (1-3) which, in turn, are easily obtained in high yield by oxidative coupling of 2,4-di-substituted phenols.[1]

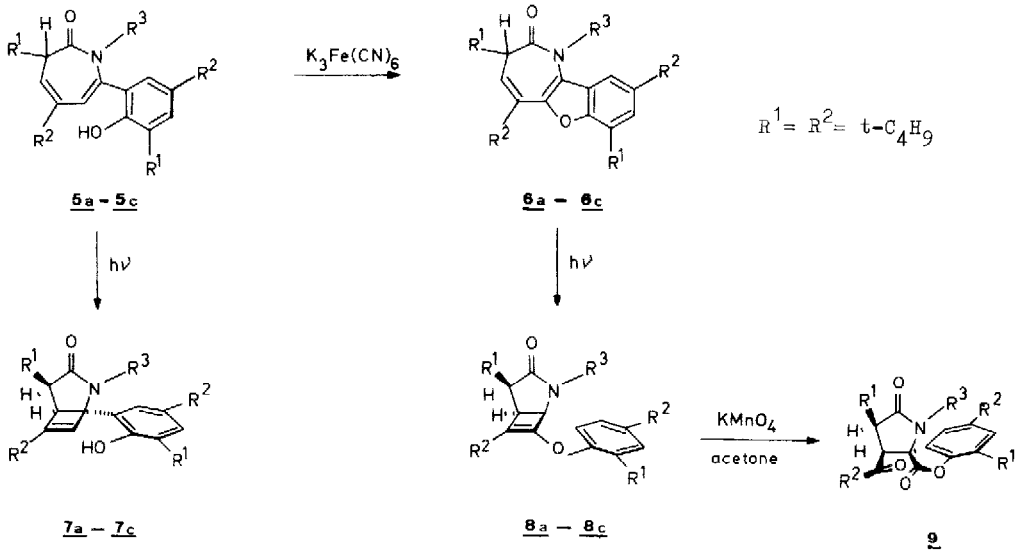
Refluxing a solution of spiroquinol ether 1 ($R^1 = R^2 = t\text{-}C_4H_9$, 4.08 g, 10 mmol) in a 1 1 1 mixture (150 ml) of methylene chloride, methanol and methylamine (40% aqueous solution) for 2 hr, followed by partial evaporation of solvent gives in 87% yield 5a as colorless crystalline precipitate



1-3 For R^1 – R^3 see Table 1 — 4 — 5a – 5g

The structure of 5a is based on elemental analysis and spectral data.[2] Photochemical reaction of 5a with $K_3Fe(CN)_6$ under nitrogen leads (via a deep green colored radical intermediate) to the benzofuranoid-annelated azepinone 6a.[3]

Thermally, azepinones 5a and 6a were found to be rather stable;[4] however, smooth photochemical valence isomerization of both 5a and 6a takes place and is in agreement with the proposed dienamide structures.[5] Thus, irradiation (Pyrex immersion well apparatus, 450 watt medium pressure mercury lamp) of 5a (2.20 g, 5 mmol) in benzene (180 ml) for 2.5 hr under nitrogen gives the isomer 7a (66%) (Conceivable symmetrical dimeric photoproducts of 5a are ruled out on the basis of an osmometric molecular weight determination). Likewise, photochemical isomerization of the arylated azepinone 6a gives 8a in 86% yield. The structures of 7a and 8a are supported by elemental analyses and



5a - 5c 6a - 6c

7a - 7c 8a - 8c 9

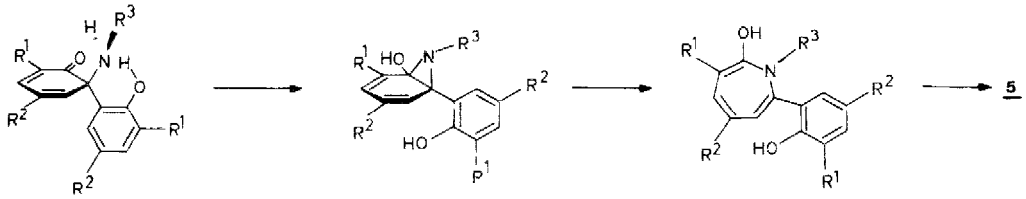
Table 1. Azepinones 5 and 6, and their Photoisomers 7 and 8

Compound	R^1	R^2	R^3	mp (°C)	Yield (%)
5a	t-C_4H_9	t-C_4H_9	CH_3	153-155	87
5b	t-C_4H_9	t-C_4H_9	n-C_3H_7	162-164	76
5c	t-C_4H_9	t-C_4H_9	c-C_6H_{11}	209-211	75
5d	t-C_5H_{11}	t-C_5H_{11}	CH_3	144-146	72
5e	t-C_5H_{11}	t-C_5H_{11}	n-C_3H_7	180-182	81
5f	t-C_4H_9	CPh_3	n-C_3H_7	211-214	90
5g	t-C_4H_9	CPh_3	c-C_6H_{11}	188-191	86
6a	R^1= R^2= t-C_4H_9		CH_3	167-168	57
6b			n-C_3H_7	190-193	78
6c			c-C_6H_{11}	237-238	97
7a			CH_3	130-143	66
7b			n-C_3H_7	133-153	93
7c			c-C_6H_{11}	138-155	83
8a			CH_3	203-205	72
8b			n-C_3H_7	136-138	71
8c			c-C_6H_{11}	181-183	95

spectroscopic data [6] Oxidation of 8a with $KMnO_4$ at room temperature gives the spiro-substituted 2(3H)-benzofuranone 9 (mp 234-235°, 92% yield) whose ^{13}C NMR spectrum reveals three carbonyl groups and whose IR spectrum exhibits the characteristic 2(3H)-benzofuranone absorption at 5.5 μ.[7]

n-Propylamine and cyclohexylamine were found to react with spiroquinol ether 1 in the same manner as described for methylamine and the resulting azepinones 5b and 5c as well as their benzofurano-annelated oxidation products 6b and 6c underwent smooth photochemical isomerization to give 7 and 8, respectively (see Table 1). Azepinones of structure 5 were also obtained in good yields by addition of primary amines to spiroquinol ethers 2 ($R^1 = R^2 = C_5H_{11}$) and 3[8] (R^1 = t-C_4H_9, $R^2 = CPh_3$).

The mechanism for the formation of azepinones 5 probably involves nucleophilic opening of the oxetene ring in 1-3 by the amine to give a 6-amino-substituted 2,4-cyclohexadienone which, as originally suggested by Paquette for the reaction of chloramine with phenolate ion,[9] isomerizes according to the following reaction sequence.

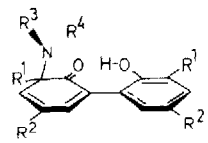


In support of this mechanism, we have found that secondary amines react with spiro quinol ethers to give 6-amino-substituted 2,4-cyclohexadienones. For example, refluxing a suspension of 1 (4.08 g, 10 mmol) in methanol (50 ml) and morpholine (5 ml) for 5 min gives a bright yellow solution from which 4 ($R^1 = R^2 =$ t-C_4H_9, $R^3 - R^4 = CH_2CH_2OCH_2CH_2$) crystallizes at room temperature (94% yield). Its structure is supported by elemental analysis and spectroscopic data [10] Interestingly, this substance is identical with a compound that had been obtained previously in the cuprous chloride-morpholine complex catalyzed oxidative coupling of 2,4-di-t-butylphenol, to which different structures, however, had been assigned.[11]

In summary, the reaction of primary amines with spiroquinol ethers, or their ortho quinonoid equivalents, to give 1,3-dihydro-2H-azepinones appears to be a general reaction. In addition, the observed smooth photochemical isomerization of the azepinones 5 and 6 confirms and extends the previously noted excited state reactivity of the conjugated diene moiety in 7-membered heterocyclic compounds [12]

References and Notes

1. a) V.V. Karpov and M.L. Khidekel, Zhur.org.Khim , 4, 861 (1968)
   b) A.S Hay and H.-D. Becker, US Patent 1,900,680 (July 31, 1969).
2. 5a Calcd for $C_{29}H_{45}NO_2$ (439.68) C,79.22, H, 10.32. Found C, 79.53, H, 10.36 IR (KBr) 3520, 3370 (broad), 1680, 1655, 1625 cm^{-1}. NMR ($CDCl_3$, δ ppm) 7.38 (d, J= 2.5 Hz, 1), 7.03 (d, J= 2.5 Hz, 1); 6.43 (d, J ≈1 Hz, 1); 5.68 (s, 1 OH); 5 62 (d, J= 6.5 Hz, 1), 2.87 (s, 3), 2.31 (br d, J= 6.5 Hz, 1), 1.45 (s, 9), 1.32 (s, 9), 1.23 (s, 9), 1 19 (s, 9)
3. This type of intramolecular oxidative coupling of a phenol, though initiated by a one-electron oxidant, most likely is the result of an electrophilic substitution of the azepine ring, involving disproportionation of the originally formed phenoxy radical. The formation of 6a supports the azepinone structure 5 and rules out the isomeric structure 11 whose precursor 10 could be formed by conjugate addition of methylamine to spiroquinol ether 1.



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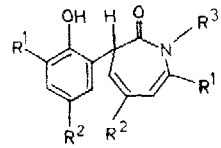

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4. Uncharged NMR spectra after 5 min at 325°.
5. Cf. L.A Paquette, J. Amer. Chem. Soc , 86, 500 (1964).
6. 7a Calcd for $C_{29}H_{45}NO_2$(439.68) C, 79.22, H, 10.32 Found C, 79 02, H, 10.31 IR (KBr) 3310 (broad), 1688 cm^{-1} NMR ($CDCl_3$, δ ppm) 7 55 (d, J= 2 5 Hz, 1), 7 03 (d, J= 2.5 Hz, 1), 6.75 (s, 1), 6.23 (s, 1), 3 59 (d, J= 9 Hz, 1), 2.97 (d, J= 9 Hz, 1), 2 73 (s, 3), 1 42 (s, 9), 1.28 (s, 9); 1 24 (s, 18).
   8a Calcd for $C_{29}H_{43}NO_2$(437 67) C, 79.58, H, 9 90. Found C, 79 60, H, 9.96 IR (KBr) 1690, 1655 cm^{-1} NMR ($CDCl_3$, δ ppm) 7 35 (d, J= 2.5 Hz, 1), 7.17 (d, J= 2 5 Hz, 1), 3 56 (d, J= 9 Hz, 1), 2 72 (d, J= 9 Hz, 1), 2 42 (s, 3), 1.42 (s, 9), 1 30 (s, 18), 1 26 (s, 9)
7. H.E. Holmquist, J. Org Chem., 34, 4164 (1969)
8. Prepared by oxidation of 2-t-butyl-4-tritylphenol($CoCl_2$-pyridine catalyst)
9. L A. Paquette and F. C. Farley, J. Amer. Chem Soc , 89, 3595 (1967).
10. Calcd for $C_{32}H_{49}NO_3$(495.75) C, 77.53, H, 9 96 Found: C, 77.26; H, 9.76. NMR ($CDCl_3$, δ ppm) 11 25 (s, 1 OH), 7 25 (d, J= 2.5 Hz, 1), 6.98 (d, J= 2.5 Hz, 1), 6.65 (d, J= 2 5 Hz, 1), 6.25 (d, J= 2.5 Hz, 1), 3 88 (m, 4), 2.70 (m, 4), 1.38 (s, 9), 1.25 (s, 9), 1.20 (s, 9), 0.93 (s, 9)
11. a) V V Karpov, V A Puchkov and M L Khidekel, Zhur.org.Khim., 4, 1594 (1968)
    b) D G Hewitt, J Chem Soc., 296 (1971)
12. Cf L.A. Paquette in J F Snyder, "Nonbenzenoid Aromatics", Vol.I, p. 249, Academic Press, New York and London 1969