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Thermal Electrocyclic Spirocyclization of *p*-Benzoquinone Imines: A Novel Synthetic Route to Trifluoromethylated Spirodiazacarbocycles

Masafumi Kobayashi, Kenji Uneyama,*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700, Japan

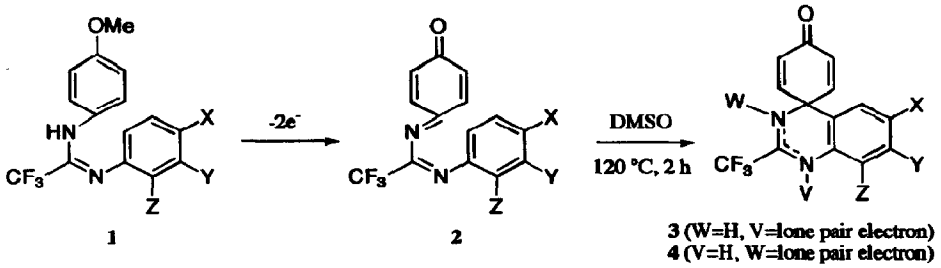
Noritaka Hamada and Setsuo Kashino*

Department of Chemistry, Faculty of Science, Okayama University, Okayama 700, Japan

Abstract: Electrochemically prepared *N*-(4-oxo-2,5-cyclohexadiene-1-ylidene)-2,2,2-trifluoroethanimidamides (p-benzoquinone derivatives) (**2**) cyclized on heating in DMSO at 120 °C to 2'-trifluoromethylspiro[2,5-cyclohexadiene-1,4'-1*H*(or 3*H*)-quinazolin]-4-ones (spirodienone derivatives) (**3**) and (**4**), which were transformed to 1,3-diazepine derivative (**7**) by Lewis acid-catalyzed dienone-phenol rearrangement.

Since azaspirodienones are potentially bioactive and interesting precursors for alkaloids,[1] carbocyclic spirodienones and azacarbocyclic spirodienones have been well documented. These spiro compounds have been prepared mostly by oxidative intramolecular spirocyclization of the corresponding phenolic derivatives,[2] photo-induced cycloaddition of dienes with *p*-benzoquinones,[3] or acid-catalyzed spirocyclization of aromatic diazoacetamides.[4] However, an effective synthesis of diazacarbocyclic spirodienones,[5] especially trifluoromethylated one is unexplored. We now report a novel electrocyclic spirocyclization of the *p*-benzoquinone imines **2** leading to the trifluoromethylated spirodiazacarbocycles **3** and **4**, and further transformation of them to the trifluoromethylated 1,3-diazepine **7**.

We previously reported that electrochemical oxidation of *N*-aryl-2,2,2-trifluoroethanimidamides **1** followed



1 **2** **3** (W=H, V=lone pair electron) **4** (V=H, W=lone pair electron)

Scheme 1

by Lewis acid-catalyzed cyclization of **2** produced *N*-aryl 2-trifluoromethylbenzimidazoles in high to excellent yields.[6]

In contrast, thermal electrocyclic reaction and proton migration proceeded predominantly on heating **2** in a polar solvent, affording spirodiazacarbocycles **3** and **4** in good yields (Scheme 1). The ^{13}C NMR spectra of **3g** showed a carbonyl group at 184 ppm and a quaternary carbon at 55 ppm, suggesting a typical spirodienone structure. X-Ray crystallographic analysis[7] revealed unequivocally the spirodienone structure of **3g**. A perspective view of the molecular structure in a hydrogen-bonded dimer is shown in Fig. 1. The products were an inseparable mixture of the two tautomers (**3** and **4**). However, the corresponding *N*-methyl compounds **3** and **4**[8] which were separable by column chromatography although the ratio of the two tautomers was changed.

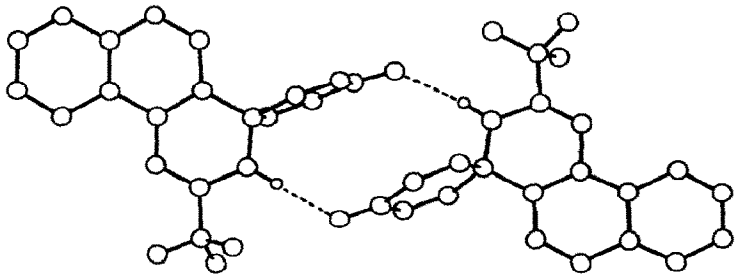


Fig. 1. X-Ray Structure of a Hydrogen-bonded Dimer of **3g**.

Table 1. Solvent Effect for the Reaction[a] of **2b**

Entry	Solvent	Temp. (°C)	Time (h)	**3b** and **4b** (% yield)
1	benzene	80	22	-[b]
2	toluene	110	18	-[c]
3	*p*-xylene	145	6	-[c]
4	DMSO	120	2	97[d]
5	MeCN	80	21	91[d]
6	*n*-BuOH	117	2	83[d]
7	EtOH	78	4	88[d]
8	AcOH	118	2	32[d], 40[e]

[a] **2b** (0.5 mmol), solvent (2 mL). [b] Recovery of **2b** (88 %). [c] A mixture of unidentified products. [d] A mixture of the two tautomers (**3b** and **4b**). [e] Yield of 1-(4-Methoxyphenyl)-2-trifluoromethyl-6-hydroxybenzimidazole.

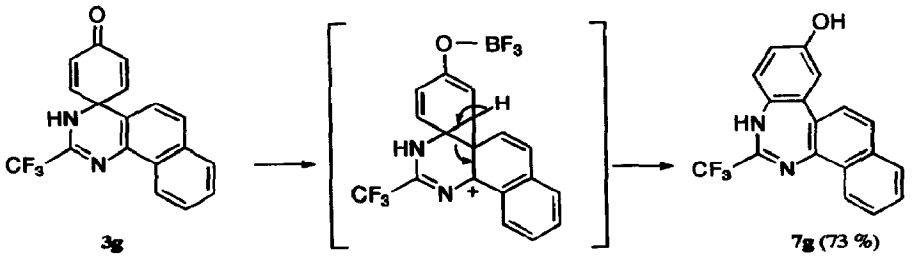
The spirocyclization was markedly affected by the polarity and acidity of the solvents (Table 1). Most of the starting material **2** was recovered on refluxing it in benzene. The reaction of **2** at higher temperature in toluene and p-xylene provided a mixture of the unidentified products. However, a clean reaction occurred smoothly in polar solvents such as DMSO and MeCN to give the desired **3** and **4** in excellent yields (entries 4 and 5 in Table 1). Protic solvents enhanced the reaction rate and were also useful for the purpose (entries 6 and 7). But, acetic acid promoted partially the acid-catalyzed benzimidazole formation (entry 8, 40 %).[6]

The results on the thermal spirocyclization of **2** in DMSO are listed in Table 2. Both compounds bearing the electron-withdrawing or electron-donating substituent on the aromatic ring provided the spiro compounds in good to excellent yields. Not only *N*-substituted phenyl group but also *N*-(naphthyl) and *N*-(5,6,7,8-tetrahydronaphthyl) groups affected the cyclization smoothly.

Table 2. Thermal Spirocyclization[a] of **2** in DMSO

Compound	X	Y	Z	**3** and **4** (%)[b]	Ratio (**3** : **4**)[c]
a	H	H	H	92	1:1
b	OMe	H	H	97	3:1
c	Me	H	H	99	11:9
d	Cl	H	H	97	1:1
e	NO_2	H	H	66	1:4
f	H	$(CH_2)_4$		84	1:2
g[d]	H	$(CH{=}CH)_2$		66[e]	1:0
h[d]	Cl	$(CH{=}CH)_2$		61[e]	1:0

[a] Reaction conditions: **2** (0.5 mmol), DMSO (2 mL), 120 °C, 2 h. [b] A mixture of two tautomers (**3** and **4**). [c] By ^{13}C NMR analysis. The detailed analytical data will be reported elsewhere. [d] After the electrolysis of **1g** or **1h**, a mixture of **3g** and **2g** or **3h** and **2h** was formed. It was converted to **3g** or **3h**, respectively on standing for 2 h at room temperature. [e] Only one tautomer (**3g**, **3h**) was formed.



3g **7g** (73 %)

Reaction Condition: **3g** (0.6 mmol), $BF_3{\cdot}Et_2O$ (1.2 mmol), toluene (6 mL), 110 °C, 2 h.

Scheme 2

The treatment of the spirodienone **3g** with $BF_3 \cdot Et_2O$ provided 1,3-diazepine derivative **7g** (73 %) via the dienone-phenol rearrangement (Scheme 2).[4,9] Detailed optimization about the reaction will be discussed elsewhere.

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7. The compound **3g** was recrystallized from benzene. Crystal data: $C_{18}H_{11}F_3N_2O$, Mr = 328.29, triclinic, $P\bar{1}$, a = 13.623 (2), b = 19.634 (4), c = 11.291 (2) Å, α = 90.59 (2), β = 98.28 (1), γ = 94.46 (2)°, V=2979 (2) $Å^3$, Z=8, D_X=1.464 g cm^{-3}. Intensity measurements were carried out for $2\theta \leq 48°$ on a Rigaku AFC5R diffractometer by using Mo Kα radiation (λ = 0.71073 Å). The structure was solved by a direct method and refined by a full-matrix least-squares method. Final R and Rω were 0.106 and 0.076, respectively, for 3041 reflections [$I_O > 3\sigma(I_O)$]. In the crystal there exist two independent NH···O hydrogen bonded dimers.
8. Reaction of a mixture of spirodienones **3b** (3H) ,**4b** (1H) (**3b**:**4b** = 3:1) with iodomethane in the presence of K_2CO_3 provided the corresponding *N*-methylated products (3-Me) and (1-Me) [(3-Me):(1-Me) = 1:1].
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