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The Reaction of 6-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylcyclohexa-2,4-dien-1-one with Benzene-1,2-diamine: Synthesis and Chemistry of *N*-(2-Aminophenyl)-2-hydroxy-5-methylbenzimidoyl Cyanide

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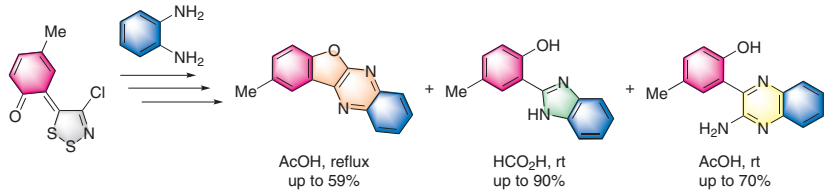
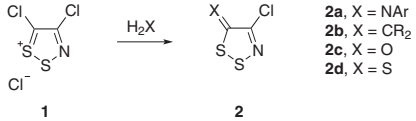


Received: 14.10.2019
Accepted after revision: 21.10.2019
Published online: 05.11.2019
DOI: 10.1055/s-0039-1690246; Art ID: st-2019-d0545-l

Abstract (*Z*)-6-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylcyclohexa-2,4-dien-1-one, readily prepared from 4,5-dichloro-1,3,4-dithiazolium chloride and *p*-cresol, reacts with benzene-1,2-diamine to give *N*-(2-aminophenyl)-2-hydroxy-5-methylbenzimidoyl cyanide. The latter, in acidic media, cyclizes to give, depending on the reaction conditions, 2-methylbenzofuro[2,3-*b*]quinoxaline, 2-(1*H*-benzo[*d*]imidazol-2-yl)-4-methylphenol or 2-(3-aminoquinoxalin-2-yl)-4-methylphenol.

Key words 1,2,3-dithiazole, imidazole, quinoxaline, benzofuran, ionizing power, carboxylic acid, heterocycle, cyclization

4,5-Dichloro-1,2,3-dithiazolium chloride (Appel salt; **1**),[1,2] prepared around 35 years ago, is the most well-known aromatic dithiazole and the starting material for many neutral 5*H*-1,2,3-dithiazoles **2** by reaction with various nucleophiles (Scheme 1).[3–6]



Scheme 1 Reaction of Appel salt **1** with nucleophiles

For example, reaction of Appel salt **1** with (hetero)aromatic amines provides access to 5*H*-1,2,3-dithiazol-5-imines **2a**, the most well studied category of neutral 1,2,3-dithiazoles to date. Several dithiazolimines **2a** display properties such as antitumor,[7] antibacterial,[8–11] antifungal,[9,12–14] and herbicidal activity.[15] Inactivation of the glutamine/amino acid transporter ASCT2,[16] and elicited pigment loss on developing Xenopus embryos[17] by 1,2,3-dithiazolimines have also recently been reported. Dithiazolimines **2a** also find use in synthesis. Recent developments include ring transformations to pyrazolo[3,4-*d*]thiazoles,[18] pyridothiazoles,[19] pyrido[2,3-*d*]pyrimidines,[20] and the rare 1,2,4-dithiazines.[21]

The synthesis and chemistry of 5*H*-1,2,3-dithiazol-5-ylidenes **2b**, which can be derived from the reaction of Appel salt **1** with either active methylene compounds or aromatic enols, are much less explored than their imine counterparts **2a**. Nevertheless, active methylene compound-derived dithiazolylidenes are numerous. Examples include ylidenemalononitrile **3**,[22–24] alkyl (dithiazolylidene)-2-cyanoacetates **4**,[1] 5-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**),[25] 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-1,1,1-trifluoropropan-2-ones **6**,[26] and 4-chloro-5-(diphenylmethylene)-5*H*-1,2,3-dithiazole (**7**)[25] (Figure 1). Dithiazolylidenes not derived from Appel salt **1** have also been reported.[27]

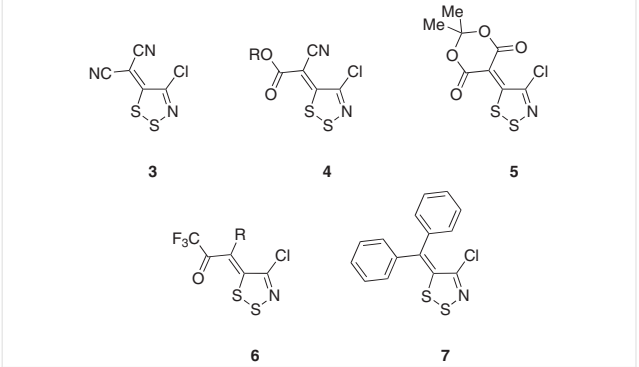


Figure 1 Structures of known 1,2,3-dithiazolylidenes

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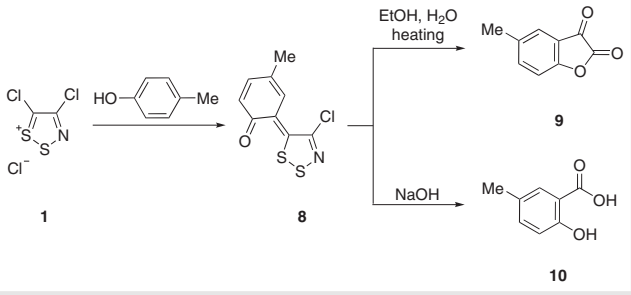
Several dithiazolylidenes undergo useful ring transformations, such as the conversion of ylidenemalononitrile **3** into 3-haloisothiazole-5-carbonitriles;[28] 2,2-dimethyl-1,3-dioxane-4,6-dione **5** into 6-carbamoyl-5-oxo-5*H*-furo[2,3-*d*][1,2,3]dithiazoles;[29] 1,1,1-trifluoropropan-2-ones **6** into 2,5-dihydro-2-iminopyrroles and furans,[30] and diphenylmethylene **7** into 3-phenylbenzo[*b*]thiophene-2-carbonitrile.[25]

In contrast to dithiazolylidenes derived from active methylene compounds, only one aromatic enol-derived dithiazolylidene was known until recently; that being (*Z*)-6-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylcyclohexa-2,4-dien-1-one (**8**). The high-yielding synthesis of ylidene **8**, from Appel salt **1** and *p*-cresol, and its hydrolysis to benzofuran-2,3-dione (**9**) and 2-hydroxybenzoic acid (**10**) were reported by Appel in 1985 (Scheme 2).[1] Since then, to our knowledge, no other ylidene **8** chemistry has been reported.



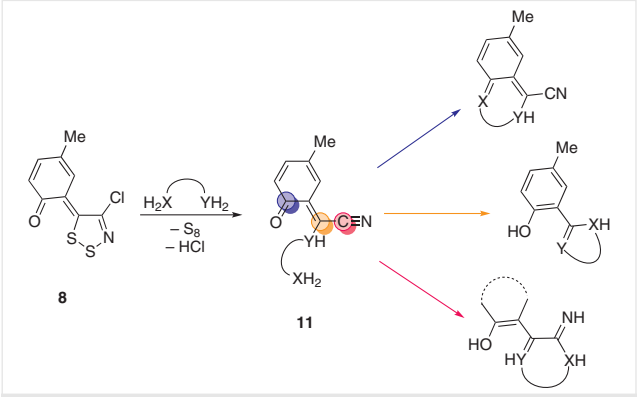
Scheme 2 Synthesis and known chemistry of (*Z*)-6-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylcyclohexa-2,4-dien-1-one (**8**)

Recently, we expanded this family of dithiazolylidenes to analogues of electron-rich pyridols,[16] and, in 2018, Thiéry et al. reported the reaction of Appel salt **1** with indolin-2-ones.[31]

The absence of additional chemistry of dithiazolylidene **8** is surprising. Compound **8** has a deep-purple color, owing partly to its *ortho*-quinone methide structure, and to a strong contribution of a charge-separated resonance form. Furthermore, it hosts a latent aromatic ring that, on reaction with nucleophiles, can be restored. We hypothesized that reaction of ylidene **8** with a nucleophile could give intermediate **11**, which has numerous electrophilic sites and, in the presence of a tethered nucleophile, at least three different products could form (Scheme 3). In light of this, we initiated studies on the reaction of ylidene **8** with bis-nucleophiles.

Herein, we report the reaction of (*Z*)-6-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylcyclohexa-2,4-dien-1-one (**8**) with benzene-1,2-diamine and reveal some preliminary chemistry of the initially formed product.

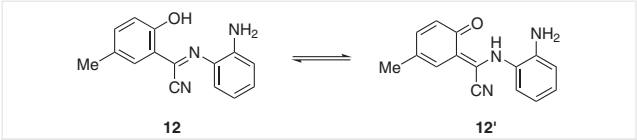
The reaction of benzene-1,2-diamine with dithiazolylidene **8** in DCM with DBU as base gave no cyclization products. Instead, a red colored product **12** was isolated



Scheme 3 Envisioned reactivity of dithiazolylidene **8** with bis-nucleophiles

that crystallized as bright-red needles from cyclohexane.[32] Mass spectrometry (*m*/*z* 252 $[M + H]^+$), and elemental analysis supported the molecular formula $C_{15}H_{13}N_3O$. FTIR spectroscopy revealed the presence of a cyano group [ν_{max} (C≡N) 2222 cm^{-1}], and two different O/N-H groups [ν_{max} (O/N-H) 3483 and 3379 cm^{-1}]. ^1H NMR spectroscopy indicated seven aromatic resonances integrating to a total of seven protons. In addition, two broad resonances corresponding to exchangeable acidic protons were observed at 12.25 (1 H) and 3.97 ppm (2 H), indicating the presence of a phenolic hydroxyl and an amino group, respectively.

Based on the data, the product was tentatively identified as *N*-(2-aminophenyl)-2-hydroxy-5-methylbenzimidoyl cyanide (**12**). Nevertheless, its red-bright color [λ_{max} 450 nm (log ε 4.03)] was intriguing and the presence of a quinoidal form **12′** could not be ruled out. To study the origin of the red color we performed TD-DFT calculations, at the B3LYP/6-311G(d,p) level of theory, for both the phenolic **12** and quinoidal form **12′** (Scheme 4).



Scheme 4 The structure of *N*-(2-aminophenyl)-2-hydroxy-5-methylbenzimidoyl cyanide (**12**) and its quinoidal form **12′**

TD-DFT calculations gave a λ_{max} of 481 nm for the phenolic form **12** and 525 nm for the quinoidal **12′**. In addition, the energy calculations showed that the phenolic form **12** is 5.9 kcal mol^{-1} more stable than the quinoidal form **12′**. These results further support the proposition that the product has the structure of phenol **12**. In addition, the TD-DFT calculations suggest that the lowest excitation energy is associated with a HOMO→LUMO transition. Analysis of the orbital distribution for the HOMO and LUMO in compound

12 revealed a charge-transfer process from the amino to the cyano group (Figure 2), which could be responsible for the bright-red color of the molecule.

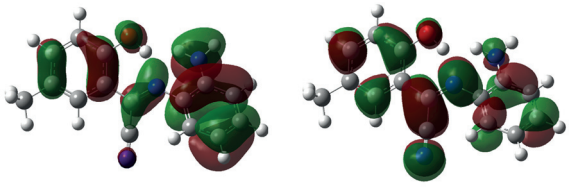
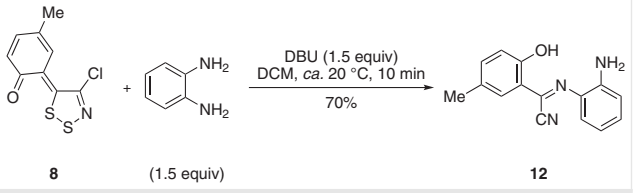


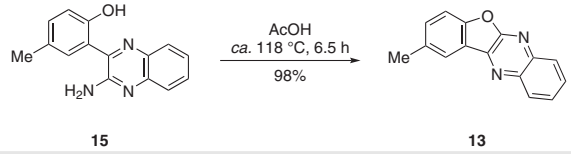
Figure 2 HOMO and LUMO molecular orbital representations for compound **12**

The reaction was partially optimized. The use of stoichiometric amounts of benzene-1,2-diamine (1 equiv) and DBU (1 equiv) led to a long reaction time (>6 h) and a moderate product yield (44%). A slight excess of benzene-1,2-diamine and DBU (1.1 or 1.25 equiv) significantly reduced the reaction time (10–15 min), but the product yield remained moderate (49% and 65%, respectively). With 1.5 equiv of DBU and benzene-1,2-diamine the reaction was complete within 10 minutes and the product was obtained in very good yield (70%; Scheme 5). Further increasing the number of equivalents (2 equiv) had no effect on product yield (5 min, 70% yield).



Scheme 5 Reaction of 1,2,3-dithiazolylidene **8** with benzene-1,2-diamine

Unable to obtain cyclization products under the above reaction conditions, we investigated the reactivity of benzimidoyl cyanide **12** in different media and interesting results were observed in neat carboxylic acids as solvent.[33] A solution of compound **12** in AcOH at room temperature gave, after four hours, three products: 2-methylbenzofuro[2,3-*b*]quinoxaline (**13**),[34] 2-(1*H*-benzo[*d*]imidazol-2-yl)-4-methylphenol (**14**)[35] and 2-(3-aminoquinoxalin-2-yl)-4-methylphenol (**15**), in <1, 23, and 62% yield, respectively (Table 1, entry 1). Increasing the reaction time (up to 14 h) did not significantly affect the product yields (entry 2). Increasing the temperature to 118 °C (refluxing AcOH) gave, as the major product, benzofuroquinoxaline **13** (62%) with a concomitant decrease in yield for the aminoquinoxaline **15** (traces) (entry 3); the yield of benzimidazole **14** remained unaffected. This indicated that aminoquinoxaline **15** was an intermediate in the formation of benzofuroquinoxaline **13**. Further support for this view was provided when a pure sample of aminoquinoxaline **15** heated in AcOH at 118 °C, gave benzofuroquinoxaline **13** in near quantitative yield (Scheme 6).

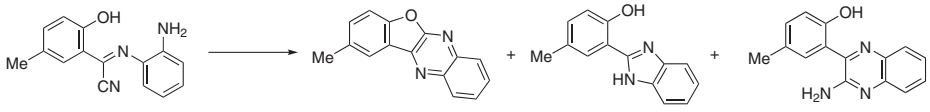


Scheme 6 Transformation of 2-(3-aminoquinoxalin-2-yl)-4-methylphenol (**15**) into 2-methylbenzofuro[2,3-*b*]quinoxaline (**13**)

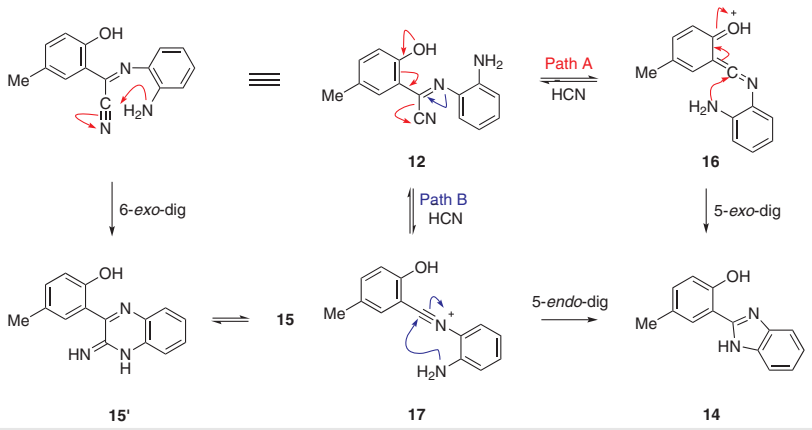
When HCO_2H was used as solvent the selectivity completely reversed and benzimidazole **14** was obtained as the main product (90% yield) with only traces of benzofuroquinoxaline **13** (Table 1, entry 4).

This switch in selectivity can be tentatively attributed to the different ionizing powers of acetic and formic acids; i.e., the ability of the solvent to promote ionization of a species by an S_N1-type process.[36] Notably, formic acid is second

Table 1 Transformations of *N*-(2-Aminophenyl)-2-hydroxy-5-methylbenzimidoyl Cyanide (**12**) in AcOH and HCO_2H



Entry	Solvent	Time (h)	Temp (°C)	Yield (%)		
				13	**14**	**15**
1	AcOH	4.17	20	trace	23	62
2	AcOH	14	20	trace	24	70
3	AcOH	5	118	59	20	trace
4	HCO_2H	1	20	trace	90	0



Scheme 7 Speculative mechanistic pathways to explain the change in selectivity observed when acetic acid is switched to formic acid

only to water in ionizing power.[36] The dramatic differences between the ionizing powers of AcOH vs. HCO_2H and the effect on reaction outcomes is well documented, for instance in the solvolysis of *cis*-cyclooctene oxide,[37] the ionization of organic chlorides,[38] and the solvolysis of 1-adamantyl iodide.[39] Based on these differences, we tentatively propose that, in the case of AcOH, the mechanism proceeds via a 6-*exo*-dig cyclization by nucleophilic attack of the amine onto the cyano group to give quinoxalinimine **15′**, whereas in HCO_2H ionization of compound **12** to the cation **16** or **17**, by assistance of the oxygen or nitrogen lone pair, respectively, precedes cyclization, which then favors exclusive formation of benzimidazole **14** (Scheme 7). Mechanistic investigations are under way to understand the observed reactivities better.

To conclude, the reaction of (*Z*)-6-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylcyclohexa-2,4-dien-1-one(**8**) with benzene-1,2-diamine gives *N*-(2-aminophenyl)-2-hydroxy-5-methylbenzimidoyl cyanide (**12**) as the major product in very good yield. In acidic media, compound **12** gives three different products: 2-methylbenzofuro[2,3-*b*]quinoxaline (**13**), 2-(1*H*-benzo[*d*]imidazol-2-yl)-4-methylphenol (**14**), and 2-(3-aminoquinoxalin-2-yl)-4-methylphenol (**15**). Each product can be formed in high yield by careful selection of solvent and temperature. The products formed are potentially useful heterocyclic scaffolds,[40] and the scope of the reaction is currently under examination.

Acknowledgment

We thank Dr Georgia A. Zissimou for the execution of the theoretical calculations.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690246.

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(32) To a stirred solution of (*Z*)-6-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylcyclohexa-2,4-dien-1-one (**8**; 20.0 mg, 0.082 mmol) and benzene-1,2-diamine (13.3 mg, 0.123 mmol) in dry DCM (5 mL) was added dry DBU (18.5 μL, 0.123 mmol, 1.5 equiv) in one portion. After complete consumption of the starting material (10 min, by TLC) the reaction mixture was poured onto a packed column of silica and purified by chromatography (*n*-hexane/DCM, 10:90) to give *N*-(2-aminophenyl)-2-hydroxy-5-methylbenzimidoyl cyanide (**12**; 14.4 mg, 70%) as bright-red needles; mp (hot stage): 151–153 °C (from cyclohexane); R_f 0.62 (DCM). Anal. Calcd (%) for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.61; H, 5.31; N, 16.54. UV: λ_{max} (DCM) = 229 (log ε 4.29), 245 (4.28), 261 (4.27), 291 (4.33), 412 inf (3.96), 450 nm (4.03). IR: 3483m, 3379m, 3034w (aryl C-H), 2924m and 2853w (alkyl C-H), 2222w (C≡N), 1628m, 1580m, 1537m, 1487s, 1458m, 1389m, 1317m, 1294m, 1275m, 1254m, 1231m, 1192m, 1157m, 1144m, 1099w, 1065w, 1034w, 1022m, 989m, 955w, 928m, 905m, 868m, 843m, 814m, 789m cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 12.25 (s, 1 H, OH), 7.67 (d, *J* = 1.0 Hz, 1 H, Ar*H*), 7.30–7.25 (m, 2 H, Ar*H*), 7.20 (dd, *J* = 8.0, 1.0 Hz, 1 H, Ar*H*), 6.97 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 8.67–8.63 (m, 2 H, Ar*H*), 2.37 (s, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s), 141.8 (s), 140.6 (s), 135.9 (d), 132.5 (s), 130.4 (d), 130.1 (d), 129.3 (s), 120.4 (d), 118.6 (d), 117.9 (d), 117.1 (s), 116.1 (d), 110.3 (s), 20.5 (q). MALDI-TOF MS: *m*/*z* (%) = 252 (100) $[M + H]^+$, 225 (75).
(33) **General procedure**: A solution of *N*-(2-aminophenyl)-2-hydroxy-5-methylbenzimidoyl cyanide (**12**; 30.0 mg, 0.12 mmol) in the appropriate carboxylic acid (3.0 mL) was stirred at the appropriate temperature (Table 1) until complete consumption of the starting material (indicated by TLC). After completion of the reaction, the mixture was poured onto crushed ice and neutralized by careful addition of aqueous $NaHCO_3$. The aqueous phase was extracted with DCM (4 × 20 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The remaining residue was adsorbed onto silica and purified by chromatography to give the corresponding products.
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