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γ-Hydroxyalkynyl Ketones as Useful Scaffolds for the Preparation of Combinatorial Libraries of Furans, Isoxazoles and Pyrazoles

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Using 5-hydroxy-hex-3-yne-2-one (**9**) as a model substrate, the utility of the γ-hydroxyl alkynyl ketone scaffold for the preparation of combinatorial libraries of furans, isoxazoles, and pyrazoles is described. The addition of hydrazoic acid to the acetylenic ketone **9** forms in a single step both 3-azido-2,5-dimethyl furan (**10**) and α,5-dimethyl-3-isoxazolemethanol (**11**). Reaction of a mixture of (*E*)- and (*Z*)-bromoenediones (**5** and **6**), accessible from 3-bromo-2,5-dimethyl furan (**17**), with 1,1-dimethylhydrazine afforded a nearly quantitative yield of 1,3-dimethyl-5-acetylpyrazole (**18**). When the (*E*)- and (*Z*)-vinyl bromides **5** and **6** were reacted with sodium azide, 3-acetyl-5-methylisoxazole (**7**) formed via the intermediate (*Z*)-3-azido-3-hexene-2,5-dione (**4**), was the only product.

Introduction

In recent years, several different approaches for the preparation of combinatorial libraries of heterocycles have been described.[1,2] Using chemistry that we developed for the synthesis of (*E*)-3-azido-3-hexene-2,5-dione (**3**),[3,4] we wish to illustrate the applicability of this methodology for the preparation of combinatorial libraries of furans[5] and isoxazoles[6] and also to illustrate the utility of the γ-hydroxyalkynyl ketone scaffold for the preparation of pyrazole libraries.[7]

γ-Hydroxyalkynyl ketones are useful starting materials for the preparation of 3-halofurans,[8] 3-methoxyfurans,[9] furonones,[9] 3-thiolfurans[10] and 3-furylcarbonyl compounds.[11] Several years ago, Katritzky reported on a general method for the preparation of γ-hydroxylalkynyl ketones by the lithiation of 1-(benzotriazol-1-yl) propargylethyl ether followed by reaction with an aldehyde. A subsequent lithiation was followed by treatment with an electrophile, such as an alkyl halide. Acidic hydrolysis and release of the benzotriazole synthetic auxiliary unmasked the latent carbonyl group. Both of these electrophilic additions were regiospecific, and because of this, the route should be amenable for the preparation of libraries of γ-hydroxyalkynyl ketones.[12] In addition, in another application, Katritzky has recently extended his solution-phase benzotriazole chemistry for use in solid-phase synthesis.[13] As a substrate for the preparation of combinatorial libraries of furans, γ-hydroxyalkynyl ketones would be particularly useful as a 1,4-addition of a nucleophile renders the resulting γ-hydroxy-α,β-unsaturated ketone in the correct oxidation state for dehydration to the corresponding 3-substituted furan.[14] In addition, this same chemistry could also produce related isoxazole alcohols by a Michael addition of hydrazoic acid, followed by thermal elimination of nitrogen from a γ-hydroxy-3-azido-*cis*-α,β-unsaturated ketone. Because our efforts in this area were initiated in order to develop a stereospecific synthesis of (*E*)-3-azido-3-hexene-2,5-dione (**3**), we also wish to enumerate on other approaches that were evaluated for the synthesis of this unstable molecule, because such information would be useful for the preparation of libraries of functionalized *cis*-enediones.

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Results and Discussion

Following the methodology developed by Hassner, two different methods were initially evaluated for the synthesis of (*E*)-3-azido-3-hexene-2,5-dione (**3**). One approach involved the addition of iodoazide to either (*Z*)- or (*E*)-3-hexene-2,5-dione (**1** and **2**), followed by elimination to yield only (*Z*)-3-azido-3-hexene-2,5-dione (**4**).[15] The other approach involved the reaction of a mixture of (*E*)- and (*Z*)-*trans*-3-bromo-3-hexene-2,5-dione (**5** and **6**) with sodium azide, to exclusively afford only the *Z* isomer **4**.[16] The *Z* isomer **4** readily decomposed to 3-acetyl-5-methyl-isoxazole (**7**)[17] at room temperature within a few hours (Scheme 1).[3,18]

In related work, L'Abbé and others had reported that the addition of hydrazoic acid to dimethylacetylene dicarboxylate resulted in a mixture of the corresponding (*E*)- and (*Z*)-vinyl azides.[19] Application of this method for the preparation of mixture of vinyl azides **3** and **4** by the reaction of 3-hexyne-2,5-dione (**8**)[17,20] with hydrazoic acid yielded only the *Z* isomer **4**. The exclusive formation of the *Z* isomer **4** in these experiments may be the result of thermodynamic control (Scheme 2).[16,21]

In contrast, reaction of 5-hydroxy-hex-3-yne-2-one (**9**)[9,20,22] with sodium azide in acetic acid yielded 85% 3-azido-2,5-dimethylfuran (**10**)[3,4] and 15% α,5-dimethyl-3-isoxazolemethanol (**11**)[23], as determined by ^{1}H NMR. Owing to the significant differences in polarity of these compounds, these components were readily separated by flash chromatography

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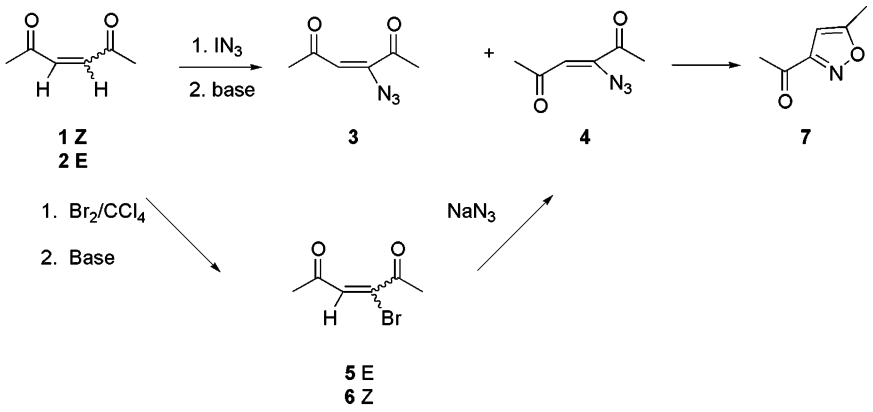
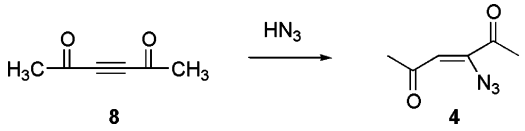
Scheme 1



Scheme 2



to ultimately afford a 53% yield of the furyl azide **10** (Scheme 3).

The obtention of both of these compounds highlights some of the problems that were observed when other standard methods for the preparation of the (*E*)-vinyl azide **3** were attempted. A Michael addition of sodium azide to the hydroxy ketone **9** results in the formation of two equilibrating isomers, **12** and **13**. The ratios of the products **10** and **11** is reflective of the fact that apparently, the rate of cyclization and dehydration of the (*E*)-vinyl azide **12** to the furyl azide **10** is faster than the rate of thermal elimination of nitrogen from the (*Z*)-vinyl azide **13** to isoxazole alcohol **11**. These acidic reaction conditions serve to enhance the observed selectivity.

In several recent publications, the use of iminophosphoranes in combinatorial synthesis has been described.[24] In our proposal for a combinatorial synthesis based on this chemistry, polymer-bound triphenylphosphine would be used to separate the furyl azide **10** from the isoxazole alcohol **11**.[25] In a model system, the furyl azide **10** was found to readily react with triphenylphosphine to yield 3-triphenylphosphine-2,5-dimethylfuryliminophosphorane (**14**) (Scheme 4).[26] This resin-capture approach would allow for a method to separate combinatorial libraries of these two very different heterocycles, namely furans and isoxazoles, while at the same time providing a functional group, the iminophosphorane, by which additional functionality could be introduced into the furan library.

As a further example of the diversity that is available from the γ-hydroxyalkynyl ketone scaffold, this chemistry was used to prepare a model pyrazole ketone. In related work in this laboratory, hydrazone **15** was required for the preparation of the quaternary salt **16** in a study of the modified Neber reaction. This compound was to be prepared by the addition of 1,1-dimethylhydrazine to diacetylacetylene (**8**). Although pyrazoles are typically prepared by the addition of a hydrazine to 1,3-dicarbonyl compounds,[27,28] it was assumed that the *gem*-dimethyl groups would block the formation of the pyrazole (Scheme 5).

Because diacetylacetylene (**8**) is not a stable compound and the preparation of gram quantities of this compound is not a trivial matter, we considered the addition of 1,1-dimethylhydrazine to either (*E*)- or (*Z*)-vinyl bromides **5** and **6** as an alternative. A Michael addition of 1,1-dimethylhydrazine followed by elimination of hydrogen bromide was expected to produce the desired hydrazone **15**. The required vinyl bromides **5** and **6** were prepared by two routes. In addition to the previously described bromination, dehydrobromination methodology, the other route employed chemistry that we developed for the synthesis of 3-azido-2,5-dimethylfuran (**10**). For this furan synthesis, hydrogen bromide in acetic acid was added to a solution of 5-hydroxyhex-3-yne-2-one (**9**) in chloroform. This addition resulted in a rapid reaction, and a nearly quantitative isolated yield of 3-bromo-2,5-dimethylfuran (**17**) was obtained. Oxidation of the furan 1**7** with *m*-chloroperoxy benzoic acid yielded the (*E*)-vinyl bromide **5** (Scheme 6).[21a]

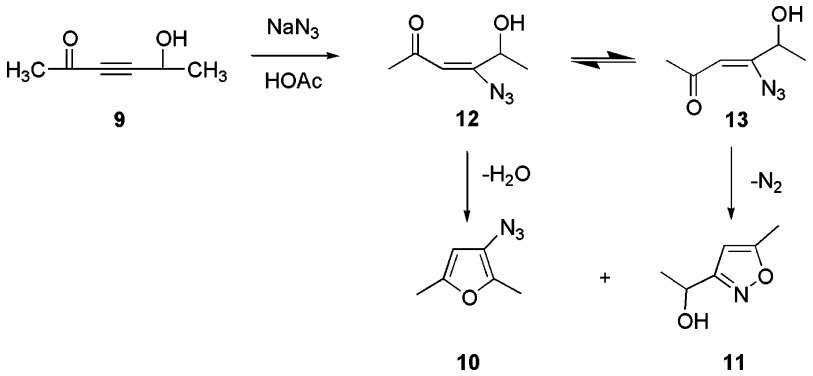
Addition of a 2-fold excess of 1,1-dimethylhydrazine to a carbon tetrachloride solution of a mixture of (*E*)- and (*Z*)-vinyl bromides **5** and **6** resulted in the immediate formation of a white precipitate. After filtration of the salt, the product was isolated by evaporation of the solvent. A nearly quantitative yield of 1,3-dimethyl-5-acetylpyrazole (**18**) was obtained. The product was characterized by ^{1}H NMR, IR, and HRMS (Scheme 7).

A likely mechanism is shown in Scheme 8 in which the aromatization of the pyrazole ring apparently facilitates the expulsion of methyl bromide. Due to the enhanced basicity of 1,1-dimethylhydrazine, as opposed to the pyrazole **18**, the excess 1,1-dimethylhydrazine functions as a trap for the methyl bromide (Scheme 8).

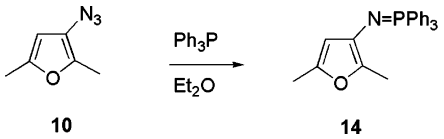
The especially high yields in this sequence, the essentially quantitative yields for the preparation of the 3-bromo-2,5-dimethylfuran (**17**), the oxidation of the furan **17** with *m*-CPBA, and the preparation of the pyrazole **18** make this chemistry particularly suitable for a solution-phase combinatorial synthesis of pyrazole ketones. In addition to the high yields, the limited number of byproducts that are produced in this synthesis, namely, water, *m*-chlorobenzoic acid,[29] and 1,1,1-trimethyl hydrazonium bromide, further enhances the applicability of this methodology for combinatorial syntheses.

In addition, this approach may also have utility in combinatorial chemistry for the preparation of solid-phase

Scheme 3



Scheme 4



pyrazole libraries. Reaction of an appropriate dialkylated resin-bound hydrazine reagent with a halo-substituted enedione may allow for a new method to prepare an *N*-alkylpyrazole ketone scaffold. For the mechanism described in Scheme 8, SN2 displacement on the quaternary ammonium cation by bromide ion should allow for differentiation of dissimilar alkyl groups when one of the alkyl groups is polymer-bound.[30] This approach may also have utility, depending on the synthesis and ease of purification of the hydrazine reagent.[31]

In summary, the utility of γ-hydroxyalkynyl ketones for the preparation of combinatorial libraries of furans and isoxazoles has been illustrated. In addition, the use of this scaffold for the stepwise conversion to pyrazole ketones is also described. Further, application of the well-known phototransformations of isoxazoles to oxazoles and pyrazoles to imidiazoles and the phototransposition reactions of furans to these libraries should allow for a method to add greater diversity to these libraries.[3,32,33]

Experimental Section

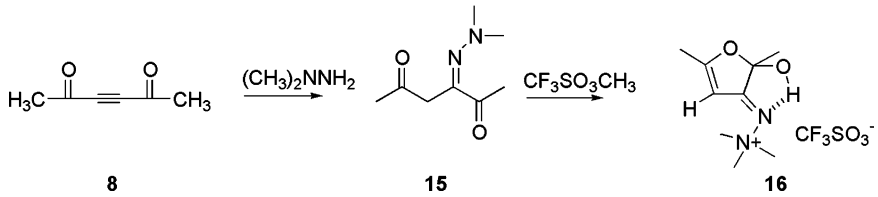
Melting points were obtained on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian model T-60 spectrophotometer in deuteriochloroform using tetramethylsilane as an internal standard. IR spectra were obtained on a Perkin-Elmer model 727 IR spectrophotometer. UV spectra were recorded on either a Perkin-Elmer UV−vis or a Cary 17D spectrophotometer. The ^{31}P NMR spectrum was obtained on a Varian model FT 80 NMR using a broad-band probe operating at 32.203 MHz. An external standard of 85% H_3PO_4 was used. Low-resolution mass spectra were obtained on a VG analytical model mass spectrophotometer, and high-resolution mass spectra were obtained on a 7070 EQ high-resolution mass spectrophotometer. Elemental analyzes were done by Robertson Laboratories, Florham, Park, NJ. A standard workup implies that the organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution and dried over magnesium sulfate.

Preparation of 5-Hydroxy-hex-3-yne-2-one (9). To a mechanically stirred solution of 34.24 g (0.3 mol) of hex-3-yne-2,5-diol in 300 mL of spectrograde acetone, which had been cooled to −10 °C, a solution of 3.2 M CrO_3 in 4 M aqueous H_2SO_4 (127 mL, 0.41 mol) was added slowly over a 2-h period.[20b] Saturated sodium chloride solution (300 mL) was added, and the supernatant was decanted. The reduced salts were washed with 600 mL of ether. The organic layer was separated, and the aqueous layer was extracted with an additional 300 mL of ether. The organic extracts were combined, and a standard workup followed. After the solvent was evaporated, the product was fractionally distilled at 58−60 °C (0.25 mm) (lit[20b] bp 57−63 °C) (0.10 mm) to afford 18.53 g (55% yield) of 5-hydroxy-hex-3-yne-2-one (**9**). ^{1}H NMR δ 1.56 (d, 3H), 2.36 (s, 3H), 4.40 (b, 1H), 4.66 (q, 1H).

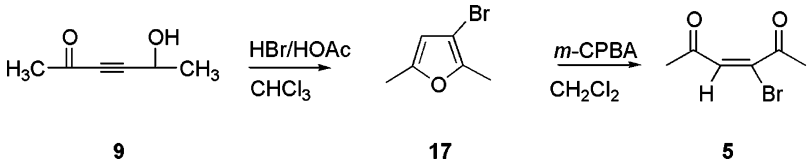
Preparation of 3-Azido-2,5-dimethylfuran (10). To 4.23 g (0.038 mol) of 5-hydroxy-hex-3-yne-2-one (**9**) in 90 mL of acetic acid, a solution of 2.64 g (0.041 mol) of sodium azide in 20 mL of water was added. The solution was placed in a freezer, which was held at −5 to −10 °C for 17 h, during which time the mixture eventually froze. Chloroform (250 mL) and water (100 mL) were added. After a standard workup, the solvent was evaporated at room temperature to yield 5.84 g of a mixture, which contained 85% of the furyl azide **10** and 15% of the isoxazole alcohol **11** as determined by ^{1}H NMR. Flash chromatography on silica gel using a mixture of 65% hexane and 35% ethyl acetate as the eluent yielded 2.71 g (53% yield) of the furyl azide **10** as a bright yellow oil. The furyl azide **10** had ^{1}H NMR δ 2.06 (s, 3H), 2.17 (s, 3H), 5.83 (s, 1H); IR (film) 4.65 (vs), 6.06 (m), 7.69 (s), 13.33 (m) μm. The furyl azide **10** is not a stable compound and polymerizes on standing.

Preparation of 3-Triphenylphosphine-2,5-dimethylfuryl Iminophosphorane (14). Under a nitrogen atmosphere and in glassware that had been washed with concentrated ammonium hydroxide and dried in an oven overnight at 120 °C, a solution of 0.1500 g (1.09 mmol) of freshly chromatographed furyl azide **10** in 2 mL of anhydrous diethyl ether was prepared. A solution of 0.286 g (1.09 mmol) of triphenylphosphine in 2 mL of anhydrous ether was added. Nitrogen evolved immediately, and a yellow solid precipitated. Additional ether was added, and under a nitrogen atmosphere, the product was filtered, and the solid was washed with anhydrous ether. The phosphinimine **14** had mp 134−136 °C (dec); ^{1}H NMR δ 2.06−2.17 (d, 6H), 5.30

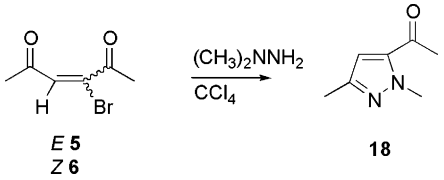
Scheme 5



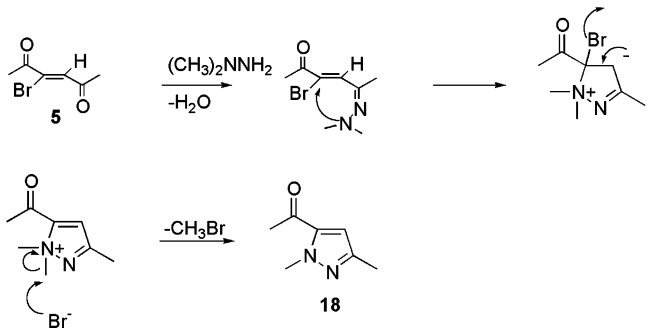
Scheme 6



Scheme 7



Scheme 8



(s, 1H), 6.83−7.90 (m, 15H); ^{31}P NMR (CH_2Cl_2) δ 4.45; IR (KBr) 6.17 (s), 6.97 (m), 7.07 (m), 7.69 (m), 9.01 (s), 14.3 (s) μm. Anal. Calcd. for $C_{24}H_{22}NOP$: C, 77.62; H, 5.97; N, 3.77; P, 8.34. Found: C, 77.49; H, 6.17; N, 4.03; P, 8.23.

Preparation of (E)- and (Z)-3-Bromo-hex-3-ene-2,5-dione (5 and 6). Under a nitrogen atmosphere and to a −10 °C solution of 3.36 g (0.03 mol) of (*Z*)-3-hex-3-ene-2,5-dione (**1**)[21a] in 20 mL of carbon tetrachloride, a solution of 4.8 g (0.03 mol) of bromine in 10 mL of carbon tetrachloride was added over a 20-min period. After the reaction was complete, as evident by ^{1}H NMR, *N*,*N*-dimethylformamide (60 mL) and 5.28 g (0.064 mol) of sodium acetate were added. The solution was stirred for 0.5 h at room temperature. Ether and water were added, and the layers were separated. After a standard workup, the product was distilled at 50−52 °C (0.2 mm) to yield 4.63 g (81% yield) of a mixture of (*E*)- and (*Z*)-vinyl bromides **5** and **6**. The *E* isomer **5** isomerizes to the *Z* isomer **6** in the presence of iodine or on standing. The (*E*)-vinyl bromide **5** had ^{1}H NMR δ 2.30 (s, 3H), 2.40 (s, 3H), 6.60 (s, 1H); the *Z* isomer **6** had ^{1}H NMR δ 2.47 (s, 3H), 2.61 (s, 3H), 7.33 (s, 1H). IR (film) (mixture) 5.85 (s), 6.36 (s), 7.35 (s), 8.33 (m), 8.26 (m), 12.8 (m) μm.

Preparation of 3-Acetyl-5-methylisoxazole (7). To a solution of 0.72 g (0.011 mol) of sodium azide in 10 mL of *N*,*N*-dimethylformamide, a solution of 48% aqueous hydrobromic acid (0.28 mL, 0.0025 mol) was added, and the mixture was held for 10 min at room temperature. The mixture of vinyl bromides **5** and **6** (0.955 g, 0.005 mol) was added, and the suspension was stirred at room temperature for 30 min. Ether (20 mL) was added, and a standard workup followed. The solvent was evaporated at reduced pressure. The (*Z*)-vinyl azide **4** had ^{1}H NMR δ 2.47 (s, 6H), 5.93 (s, 1H); IR (CCl_4) 4.65 (vs), 5.88 (s), 6.02 (m), 6.29 (m) μm. UV (CH_3CN) ϵ at 400 nm, ∼46; λ_{max} = 312 nm (ϵ = 11 700). After the solvent was evaporated, 35 mL of either methanol or acetonitrile was added. These solutions were held in the dark at room temperature for 4 h. Analysis by ^{1}H NMR revealed that the isoxazole ketone **7** was the only component present.[17] Alternatively, the ketone **7** could be prepared by the following method. A solution of the vinyl bromides **5** and **6** (0.60 g, 3.1 mmol) in *N*,*N*-dimethylformamide (2 mL) was heated to reflux, and this was followed by the addition of a solution of sodium azide (20 mg, 0.31 mmol) in *N*,*N*,-dimethylformamide (0.5 mL). Nitrogen evolved immediately, and the reaction was cooled. Water and ether were added, and the layers were separated. The ether layer was washed with additional water, and the organic layer was dried over magnesium sulfate. A ^{1}H NMR spectrum revealed that the isoxazole ketone **7** was the only component present. 3-Acetyl-5-methylisoxazole (**7**) had ^{1}H NMR δ 2.50 (s, 3H), 2.60 (s, 3H), 6.30 (s, 1H); IR (film) 5.88 (s), 6.25 (m), 6.85 (m), 7.35 (m), 7.87 (m), 8.47 (s), 8.70 (m) μm. UV (CH_3CN) λ = 306 nm (ϵ = 77.5), λ = 245 (ϵ = 1950). An authentic sample of ketone **7** was prepared by the nitrosation of 2,5-hexanedione followed by cyclization; bp 73−77 °C (13 Torr)[17] (lit[34] bp 76−77 °C (19 Torr).

Preparation of 3-Bromo-2,5-dimethylfuran (17). To a −10 °C solution of 1.12 g (0.01 mol) of 5-hydroxy-hex-3-yne-2-one (**9**) in 15 mL of chloroform, 2.5 mL of a 4.1 M hydrogen bromide in acetic acid solution (10.3 mmol) was added over a 10-min period. The appearance of water was noted immediately, and the reaction was held for 10 min. After a standard workup, the solvent was removed at atmospheric pressure. There was obtained 1.71 g (98% yield) of 3-bromo-2,5-dimethylfuran (**17**) as a nearly colorless oil. An analytical sample was prepared via distillation at 70−72 °C and 47 mm. The furan **17** had ^{1}H NMR δ 2.23 (s, 6H), 5.90 (s, 1H); IR (film) 5.85 (m), 5.95 (m), 8.21 (s), 9.24 (s),

12.7 (m) μm. Anal. Calcd. for C_6H_7BrO: C, 41.17; H, 4.03. Found: C, 41.10; H, 4.18.

Preparation of (E)-3-Bromohex-3-ene-2,5-dione (5). To 0.31 g (1.77 mmol) of 3-bromo-2,5-dimethylfuran (**17**) in 10 mL of methylene chloride, which had been cooled to −10 °C, 0.40 g (∼1.97 mmol) of technical grade *m*-chloroperoxybenzoic acid was added.[21a] The suspension was held for 2 h, the batch was filtered, and the cake was washed with methylene chloride. After a standard workup, the solvent was evaporated. There was obtained 0.33 g (98% yield) of the (*E*)-vinyl bromide **5**. An analytical sample was prepared by a molecular distillation at 25−30 °C (0.05 mm). Exact mass calcd. for $C_6H_7BrO_2$: 189.962 940 6. Found: 189.962 420 0. MS, *m*/*z* 190 (10%) (The M + 2 peak was equal in height to M^+), 175 (100%), 147 (22%), 133 (43%), 111 (37%), 104 (7%), 95 (7%), 68 (34%). The ^{1}H NMR spectrum matched one set of the peaks in the above-mentioned mixture.

Preparation of 1,3-Dimethyl-5-acetylpyrazole (18). To a 0 °C solution of 0.96 g (5 mmol) of an *E* and *Z* mixture of 3-bromo-hex-3-ene-2,5-dione (**5** and **6**) in 10 mL of carbon tetrachloride, 0.76 mL (10 mmol) of 1,1-dimethylhydrazine in 3 mL of carbon tetrachloride was added over a 10-min period. The suspension was held for an additional 10 min at ambient temperature. The mixture was filtered, and the solvent was removed. Methylene chloride was added, and the organic layer was washed with saturated sodium chloride solution. Drying over magnesium sulfate was followed by evaporation of the solvent to yield 0.66 g (96% yield) of 1,3-dimethyl-5-acetylpyrazole (**18**). An analytical sample was prepared via flash chromatography using a mixture of 65% hexane and 35% ethyl acetate as the eluent. ^{1}H NMR δ 2.27 (s, 3H), 2.43 (s, 3H), 4.10 (s, 3H), 6.56 (s, 1H); IR (CCl_4) 5.95 (s), 6.85 (m), 6.99 (s), 8.07 (s) μm. Exact mass calcd for $C_7H_{10}N_2O$: 138.079 313 0. Found: 138.079 310 0. MS, *m*/*z* 138 (69%), 123 (100%), 95 (6%).

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