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# Methyl β-(Benzotriazol-l-yl) vinyl Ketone: A New p-Acetylvinyl Cation Equivalent

Alan R. Katritzky [a] , Torsten Blitzke [a] & Jianqing Li [a]
[a] Center for Heterocyclic Compounds, Department of Chemistry , University of Florida , Gainesville, FL, 32611-7200, USA
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# METHYL β-(BENZOTRIAZOL-1-YL)VINYL KETONE: A NEW β-ACETYLVINYL CATION EQUIVALENT

**Alan R. Katritzky*, Torsten Blitzke and Jianqing Li**

Center for Heterocyclic Compounds, Department of Chemistry,
University of Florida, Gainesville, FL 32611-7200, USA



ABSTRACT: A simple and efficient two-step approach to methyl β-(benzotriazol-1-yl)vinyl ketone **7** is described. The synthetic utility of compound **7** has been demonstrated by nucleophilic substitutions of the benzotriazolyl group with a range of nucleophiles. Thus, methyl β-(benzotriazol-1-yl)vinyl ketone provides a new β-acetylvinyl cation equivalent.

β-Acylvinyl cation equivalents **1** are important synthetic intermediates[1-2] and a variety of such β-substituted enones have been investigated as synthon equivalents for **2** (Block 1).[1-3] Among methyl β-substituted vinyl ketones, methyl β-chlorovinyl ketone and methyl β-sulfonylvinyl ketone seem to be most appropriate for nucleophilic displacement due to the good leaving ability of their chloro- and sulfonyl- groups. However, methyl β-chlorovinyl ketone was reported to be highly lachrymatory, strongly vesicant and quite unstable.[1] Methyl β-sulfonylvinyl ketone has been prepared in a two-step sequence by the

* To whom correspondence should be addressed

1 2

X = OAc, OR, $OPO(OR)_2$, $NR_2$, SR, $OSO_2Ar$, Halide

Block 1



addition of tosyl iodide to methyl vinyl ketone,[4] but its nucleophilic substitution, especially with carbon nucleophiles, has not yet been extensively examined.[4-5]

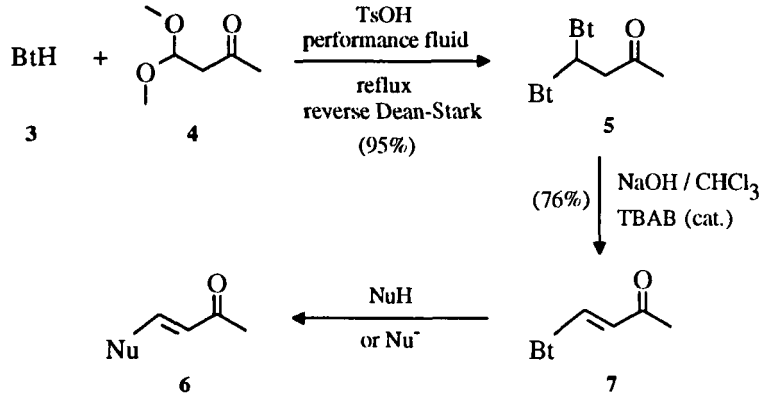
During the last decade, benzotriazole has been extensively used as a synthetic auxiliary in our laboratory and its advantageous reactivity has been well documented.[6-8] We now report a convenient synthesis of methyl β-(benzotriazol-1-yl)vinyl ketone (**7**) and nucleophilic substitutions of its benzotriazolyl group with a range of nucleophiles.

4,4-Di(benzotriazol-1-yl)-2-butanone (**5**) was readily obtained in 95% isolated yield by heating under reflux for 10 h an equimolar mixture of benzotriazole (0.2 mol) (**3**) and 4,4-dimethoxy-2-butanone (0.1 mol) (**4**) in 100 mL performance fluid,[9] in the presence of a catalytic amount of *p*-toluenesulfonic acid and using a reverse Dean-Stark (Scheme 1). Treatment of compound **5** in chloroform with 10% sodium hydroxide solution in the presence of a catalytic amount of *tetra*-butylammonium bromide (TBAB) at room temperature for 15 mins afforded methyl β-(benzotriazol-1-yl)vinyl ketone (**7**) in 76% isolated yield. The base-assisted elimination of compound **5** occurs stereo-specifically to form methyl (*E*)-β-(benzotriazol-1-yl)vinyl ketone (**7**); no Z-isomer was detected by $^1H$ NMR or by GCMS. Unlike the chloro analog,

compound **7** is a stable crystalline solid. Although methyl β-dialkylaminovinyl ketones are easily prepared in a one pot procedure by refluxing a dialkylamine and 4,4-dimethoxy-2-butanone (**4**) in methanol,[10] this procedure failed to provide methyl β-(benzotriazol-1-yl)vinyl ketone (**7**).

Since the benzotriazolyl moiety is a good leaving group, methyl β-(benzotriazol-1-yl)vinyl ketone (**7**) can be used as a β-acetylvinylating agent. We examined nucleophilic substitution reactions of **7** with various N-, S- and C-nucleophiles at 20 °C as shown in Scheme 1 and Table 1. Reactions of compound **7** with secondary amines without addition of a base gave the expected products **6a** and **6b** in high yields. Sodium thiophenolate reacted smoothly with **7** in methylene chloride to afford a mixture of E- and Z-isomers of **6c** in a ratio of 72 : 28. All carbon nucleophiles bearing one acidic proton were first deprotonated with sodium hydride and then treated with compound **7** to form E-isomers **6d**, **6e** and **6f**, respectively, in moderate yields. The reactions of **7** with other carbon nucleophiles bearing two active protons were unsuccessful.

The structures of compounds **6** were elucidated by $^{1}H$ and $^{13}C$ NMR spectra, combustion analyses (see experimental) and comparison of boiling points with literature data (Table 1). The coupling constants for *trans*-olefin protons were in the range between 12.9 Hz and 16.5 Hz. The chemical shifts of the carbonyl groups were at δ 194.5 - 197.8. Interestingly, the $\underline{C}H_2N\underline{C}H_2$ carbons of compounds **6a** and **6b** appeared on the $^{13}C$ NMR spectra as broad signals at δ 48.2 - 49.7 and at δ 42.2 - 54.2 respectively, which were confirmed by quantitative $^{13}C$ NMR spectra.




Bt = benzotriazol-1-yl

NuH = morpholine (**6a**), piperidine (**6b**), thiophenol (**6c**), 2-nitropropane (**6d**), diethyl methylmalonate (**6e**), α-methylphenylacetonitrile (**6f**)

Scheme 1

Table 1. Preparation of β-Substituted Vinyl Ketones (**6**).

| compd. | nucleophile | solvent | time (h) | yield (%)[a] | bp ($^0$C / mmHg) |
|---|---|---|---|---|---|
| **6a** | morpholine | $CH_2Cl_2$ | 2 | 90 | 125-130 / 0.3 |
| **6b** | piperidine | $CH_2Cl_2$ | 18 | 82 | 100-105 / 0.1[b] |
| **6c** | sodium thiophenolate | $CH_2Cl_2$ | 48 | 80[c] | 110-115 / 0.3[d] |
| **6d** | 2-nitropropane | DMF | 12 | 45 | 70-75 / 0.3 |
| **6e** | diethyl methylmalonate | DMF | 12 | 45 | 80-85 / 0.2 |
| **6f** | phenylbutyronitrile | DMF | 12 | 40[e] | 120-124 / 0.2 |

[a] Isolated by distillation; [b] Lit.[4] bp 156 / 7; [c] Overall yield of Z- and E-isomers; [d] Lit.[4] bp 126-129 / 2; [e] Isolated by column chromatography.

In conclusion, methyl β-(benzotriazol-1-yl)vinyl ketone **7** can be prepared in high yield from commercially available starting materials in a two-step procedure. The reactivity of this novel reagent with a range of nucleophiles has been investigated and it has been demonstrated that compound **7** can be used as an alternative β-acetylvinyl cation equivalent to the β-chloro and β-sulphonyl analogs.



## EXPERIMENTAL SECTION

Melting points were determined with a hot stage apparatus and are uncorrected. $^1$H NMR spectra were recorded using $CDCl_3$ as the solvent with tetramethylsilane as the internal standard for $^1$H (300 MHz) or solvent as the internal standard for $^{13}$C (75 MHz). Microanalyses were carried out within the department.

**4,4-Di(benzotriazol-1-yl)-2-butanone (5).**

A mixture of benzotriazole (**3**) (23.8 g, 200 mol) and 4,4-dimethoxy-2-butanone (**4**) (13.2 g, 100 mol) was heated under reflux together with 100 mL performance fluid (PF-5080) in a 250 mL round bottom flask fitted with reversed Dean-Stark device. After refluxing for 12 h, *p*-toluenesulfonic acid monohydrate (0.38 g, 2 mmol) was added to the mixture and reflux was continued for another 10 h. The reaction mixture was allowed to cool to room temperature. The crude product was separated from the performance fluid by filtration and purified by recrystallized from acetonitrile to afford the product (**5**) (29 g, 95%). White prisms, mp 179-181 °C. $^1$H NMR: δ 2.35 (s, 3 H), 4.41 (d,

$J$ = 6.9 Hz, 2 H), 7.33 (t, $J$ = 7.7 Hz, 2 H), 7.46 (t, $J$ = 7.7 Hz, 2 H), 7.74 (d, $J$ = 8.4 Hz, 2 H), 8.01 (d, $J$ = 8.3 Hz, 2 H), 8.21 (t, $J$ = 6.9 Hz, 1 H); $^{13}$C NMR: δ 30.0, 44.7, 66.5, 109.8, 120.2, 124.7, 128.5, 131.7, 146.4, 201.7. $C_{16}H_{14}N_6O$ requires: C, 62.74; H, 4.61; N, 27.43. Found: C, 63.03; H, 4.47; N, 27.64.

**(*E*)-4-(Benzotriazol-1-yl)-3-butene-2-one (7).**

To a mixture of 4,4-di(benzotriazol-1-yl)-2-butanone (**5**) (22 g, 70 mmol), and *tetra*-butylammonium bromide (1.61 g, 5 mmol) in chloroform (80 mL) was added 10% sodium hydroxide solution (80 mL). The reaction mixture was stirred at room temperature for 15 mins. The organic phase was separated, washed with 5% sodium hydroxide (3 x 80 mL) and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to give a black solid which was recrystallized twice from acetonitrile to afford the product (**7**) (10 g, 76%). White plates, mp 119-120°C. $^1$H NMR: δ 2.47 (s, 3 H), 7.10 (d, $J$ = 14.4 Hz, 1 H), 7.50 (t, $J$ = 7.7 Hz, 1 H), 7.65 (t, $J$ = 7.7 Hz, 1 H), 7.76 (d, $J$ = 8.3 Hz, 1 H), 8.14 (d, $J$ = 8.3 Hz, 1 H), 8.41 (d, $J$ = 14.4 Hz, 1 H); $^{13}$C NMR: δ 29.0, 110.2, 115.5, 120.8, 125.5, 129.4, 131.6, 133.7, 146.6, 196.3. $C_{10}H_9N_3O$ requires: C, 64.16; H, 4.85; N, 22.44. Found: C, 64.29; H, 4.69; N, 22.42.

**General Procedure for the Preparation of 6a-c.**

An appropriate nucleophile (see Table 1) (5 mmol) was added to a solution of compound (**7**) (0.94 g, 5 mmol) in methylene chloride (30 mL) at room temperature. The reaction mixture was stirred for 2 h. The solvent was removed under reduced pressure to give an oil which was purified by distillation to afford product **6a** or **6b** or **6c** (Table 1).

**(*E*)-4-Morpholino-3-butene-2-one (6a).** Yellow oil. $^1$H NMR: δ 2.10 (s, 3 H), 3.28 (t, *J* = 5.0 Hz, 4 H), 3.71 (t, *J* = 5.0 Hz, 4 H), 5.19 (d, *J* = 13.0 Hz, 1 H), 7.38 (d, *J* = 13.0 Hz, 1 H); $^{13}$C NMR: δ 27.7, 48.2-49.7 (br.s, 2 C), 65.7, 96.8, 150.8, 195.1. $C_8H_{13}NO_2$ requires: C, 61.91; H, 8.44; N, 9.02. Found: C, 61.98; H, 8.85; N, 9.39.

**(*E*)-4-Piperidino-3-butene-2-one (6b).** Yellow oil. $^1$H NMR: δ 1.60-1.63 (m, 6 H), 2.09 (s, 3 H), 3.21-3.29 (m, 4 H), 5.15 (d, *J* = 12.9 Hz, 1 H), 7.43 (d, *J* = 12.9 Hz, 1 H); $^{13}$C NMR: δ 23.7, 25.2, 27.5, 42.2-54.2 (br.s, 2 C), 95.5, 151.3, 195.2.

**4-Phenylthio-3-butene-2-one (6c).** Yellow oil, isolated as a mixture of E- and Z-isomers in a ratio of 72:28.. E-isomer: $^1$H NMR: δ 2.18 (s, 3 H), 6.00 (d, *J* = 15.3 Hz, 1 H), 7.34-7.50 (m, 5 H), 7.70 (d, *J* = 15.3 Hz, 1 H); $^{13}$C NMR: δ 27.4, 124.8, 129.6, 130.7, 132.8, 146.7, 148.9, 194.5. Z-isomer: $^1$H NMR: δ 2.27 (s, 3 H), 6.38 (d, *J* = 9.6 Hz, 1 H), 7.25 (d, *J* = 9.6 Hz, 1 H), 7.34-7.50 (m, 5 H); $^{13}$C NMR: δ 29.9, 120.0, 128.1, 129.1, 129.2, 130.2, 136.9, 196.4.

**General Procedure for the preparation of 6d-f.**

A mixture of sodium hydride (0.15 g, 80% dispersion in mineral oil, 5 mmol) and an appropriate nucleophile (see Table 1) (5 mmol) in DMF (20 mL) was stirred at room temperature for 45 mins. Compound **7** (0.93 g, 5 mmol) was added and the mixture was stirred at room temperature for another 12 h. The solvent was removed under reduced pressure to give an oil which was purified by distillation or column chromatography to afford the product **6d** or **6e** or **6f**.

**(*E*)-5-Methyl-5-nitro-3-hexen-2-one (6d).** Yellow oil, purified by distillation. $^1$H NMR: δ 1.78 (s, 6 H), 2.33 (s, 3 H), 6.23 (d, *J* = 16.3 Hz, 1 H), 7.03 (d, *J* =

16.3 Hz, 1 H); $^{13}C$ NMR: δ 25.5, 27.4, 87.1, 130.2, 143.6, 197.3. $C_7H_{11}NO_3$ requires: N, 8.90. Found: N, 8.55.

**(*E*)-5,5-Di(ethoxy carbonyl)-3-hexen-2-one (6e).** Yellow oil, purified by distillation. $^1H$ NMR: δ 1.28 (t, *J* = 7.1 Hz, 6 H), 1.61 (s, 3 H), 2.32 (s, 3 H), 4.24 (q, *J* = 7.1 Hz, 4 H), 6.13 (d, *J* = 16.5 Hz, 1 H), 7.18 (d, *J* = 16.5 Hz, 1 H); $^{13}C$ NMR: δ 13.9, 20.0, 27.0, 55.7, 62.0, 131.0, 143.7, 169.6, 197.8. $C_{12}H_{18}O_5$ requires: C, 59.49; H, 7.49. Found: C, 59.74; H, 7.86.

**(*E*)-5-Phenyl-5-cyano-3-hepten-3-one (6f).** Yellow oil, separated by column chromatography using hexane/ethyl acetate (2:1) as the eluent. $^1H$ NMR: δ 1.04 (t, *J* = 7.4 Hz, 3 H), 2.05-2.26 (m, 2 H), 2.28 (s, 3 H), 6.53 (d, *J* = 15.7 Hz, 1 H), 6.78 (d, *J* = 15.7 Hz, 1 H), 7.34-7.46 (m, 5 H); $^{13}C$ NMR: δ 9.4, 28.3, 32.6, 50.1, 119.3, 125.9, 128.3, 129.1, 129.9, 136.6, 143.5, 196.6. $C_{14}H_{15}NO$ requires: C, 78.84; H, 7.09; N, 6.56. Found: C, 79.08, H, 7.34; N, 6.86.

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