A Novel Synthesis of Alkyl, Aryl, Alkenyl, and Alkynyl 1,6-Diketones

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Introduction

1,6-Diketones are somewhat more difficult to synthesize than other types of diketones.[1] Some symmetrical alkyl 1,6-diketones have been synthesized *via* bimolecular reduction of alkyl vinyl ketones using sodium or magnesium.[2] Both alkyl and aryl symmetrical 1,6-diketones are obtained by reacting cadmium alkyls with adipoyl chloride.[3] Siloxycyclopropanes,[4] 1,2-diacylcyclobutanes,[5] and the coupling of vinyl Grignards[6] have also been used to prepare symmetrical 1,6-diketones. Maekawa *et al*. have made symmetrical 1,6-diketones by electrolysis of enol acetates.[7] Few methods are available for the synthesis of unsymmetrical 1,6-diketones; in 1985, van Leusen *et al*. synthesized both symmetrical and unsymmetrical alkyl and aryl 1,6-diketones by reactions of tosylmethyl isocyanide derivatives with 1,4-dihalides, followed by hydrolysis.[8]

Recently, we have found that some α-benzotriazole ethers can be used as masked acyl anions and can be used to synthesize alkyl,[9] aryl,[10] alkenyl,[11] and alkynyl[12] ketones. We now show that α-benzotriazole ether moieties can be used successively as two acyl anion synthons to synthesize both symmetrical and unsymmetrical alkyl, aryl, alkenyl, and alkynyl 1,6-diketones.

Results and Discussion

The two acidic α-methylene protons of 1-(phenoxymethyl)benzotriazole (**1**) were used successfully in double-lithiation techniques with considerable flexibility[9] (Scheme 1). After treatment with *n*-butyllithium at −78 °C, 1-(phenoxymethyl)benzotriazole (**1**) reacted easily with isopentyl bromide or benzyl bromide to form 1-(benzotriazol-1-yl)-4-methyl-1-phenoxypentane (**2a**) and 1-(benzotriazol-1-yl)-1-phenoxy-2-phenylethane (**2b**), respectively, in excellent yields. Compounds **2a** and **2b** were then used as alkylacyl anion synthons after their second active proton was lithiated. Under the action of *n*-butyllithium, 2 equiv of **2a** or **2b** reacted readily with 1,4-dibromobutane to form the corresponding bis-benzotriazole intermediates **4a** and **4b**, which undergo successive hydrolysis using dilute hydrochloric acid to produce the symmetrical alkyl 1,6-diketones **5a** and **5b**, respectively, in 83−84% yields.

(Benzotriazole-1-yl)methoxymethylbenzene (**3a**), *N*-(α-ethoxyallyl)benzotriazole (**3b**), and 1-(benzotriazol-1-yl)-propargyl ethyl ether (**3c**) were chosen for study as typical aryl-, alkenyl-, and alkynylacyl equivalents, respectively.[10−12] Addition of 2 equiv of *n*-butyllithium to mixtures of 2 equiv of **3a**−**c** with 1,4-dibromobutane, followed by subsequent mild oxalic acid hydrolysis, gave the expected symmetrical aryl **5c**, alkenyl **5d**, and alkynyl **5e** 1,6-diketones in 81−85% yields.

For the preparation of unsymmetrical 1,6-diketones, compounds **3a**, **2c**, or **3c** were reacted in the presence of *n*-butyllithium with excess 1,4-dibromobutane to form 1-(benzotriazol-1-yl)-5-bromo-1-methoxy-1-phenylpentane (**6a**), 3-(benzotriazol-1-yl)-7-bromo-3-phenoxyheptane (**6b**), and 3-(benzotriazol-1-yl)-7-bromo-3-ethoxy-1-phenyl-1-heptyne (**6c**), respectively, in 76−91% yields (Scheme 2). Compounds **6a**−**c** decomposed gradually at room temperature, and in particular, the decomposition of **6c** was accelerated by silica gel. However, **6a**−**c** can be stored at 0 °C. Under the action of *n*-butyllithium, **6a**−**c** reacted smoothly in a second lithiation−alkylation with a variety of benzotriazole ethers **3** to form dibenzotriazole intermediates **7**, which then underwent hydrolysis to give various unsymmetrical 1,6-diketones **8a**−**g** (Table 1).

For the dibenzotriazole intermediates **7**, the two ends derived from different benzotriazole ethers had different susceptibility toward hydrolysis: a 1-alkyl substituted moiety was more difficult to hydrolyze than that substituted with a functional group. When both ends of dibenzotriazole intermediate **7** were alkyl substituted, the hydrolysis was carried out using dilute hydrochloric acid in methanol, and the unsymmetrical dialkyl 1,6-diketones **8a** and **8b** were thus obtained in 82−86% yield. When both ends were functional group substituted, mild hydrolysis using a mixture of oxalic acid, water, and silica gel in dichloromethane was applied, because hydrolysis with dilute hydrochloric acid gave complex mixtures, and isolation was difficult. In this manner, the unsymmetical

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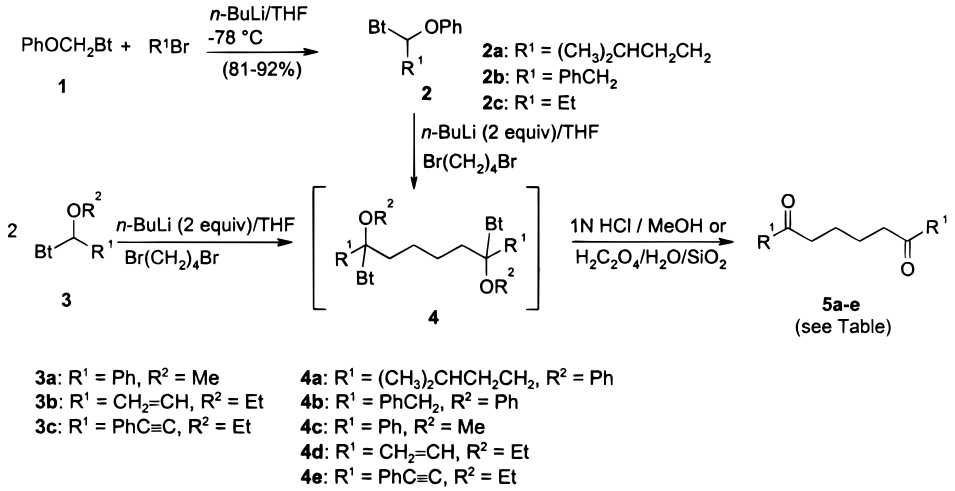
Scheme 1. Preparation of Symmetrical 1,6-Diketones



Scheme 2. Preparation of Unsymmetrical 1,6-Diketones

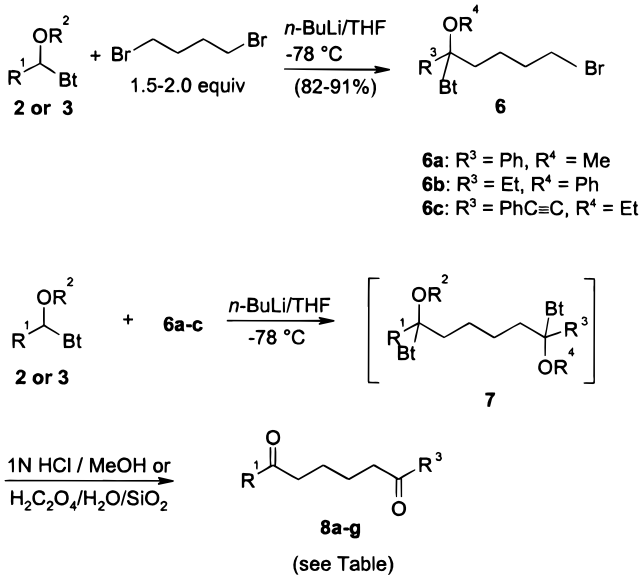


Table 1. Preparation of 5a−e and 8a−g

compd	R^1	R^3	yield (%)	molecular formula	mp (°C)
5a	$(CH_3)_2CHCH_2CH_2$		82	$C_{16}H_{30}O_2$	41−42
5b	$PhCH_2$		83	$C_{20}H_{22}O_2$	134−136
5c	Ph		82	$C_{18}H_{18}O_2$	106−107
5d	CH_2=CH		83	$C_{10}H_{14}O_2$	oil
5e	PhC≡C		81	$C_{22}H_{18}O_2$	99−100
8a	$(CH_3)_2CHCH_2CH_2$	Et	86	$C_{13}H_{24}O_2$	40−41
8b	$PhCH_2$	Et	82	$C_{15}H_{20}O_2$	39−40
8c	Et	Ph	84	$C_{14}H_{18}O_2$	36−37
8d	CH_2=CH	Ph	82	$C_{14}H_{16}O_2$	31−32
8e	PhC≡C	Et	82	$C_{16}H_{18}O_2$	oil
8f	PhC≡C	Ph	74	$C_{20}H_{18}O_2$	59−60
8g	CH_2=CH	PhC≡C	80	$C_{16}H_{16}O_2$	oil

aryl alkenyl **8d**, aryl alkynyl **8f**, and alkenyl alkynyl 1,6-diketones **8g** were synthesized in 80−86% yields. If one end was alkyl group substituted and the other end was functional group substituted, we found it advantageous if the mild conditions were first employed, and thus, the hydrolysis occurred in the functional group substituted end with high regioselectivity. Further hydrolysis by dilute hydrochloric acid then produced the alkyl aryl **8c** and alkyl alkynyl 1,6-diketones **8e** in 80−86% overall yields.

In conclusion, we have found that α-benzotriazole ethers **2** or **3** can readily undergo lithiation−alkylation, and the succeeding hydrolyses then proceed almost quantitatively. The total yields for the two step reaction are satisfactory for the synthesis of 1,6-diketones. The present method is suitable for the synthesis of a wide variety of simple and functionalized, symmetrical and unsymmetrical 1,6-diketones **5a**−**e** and **8a**−**g**. All the functionalized symmetrical and unsymmetrical 1,6-diketones have not been reported previously in the literature. These functionalized 1,6-diketones offer potentially valuable applications in organic synthesis. The starting materials used in this synthesis are readily available substituted benzotriazoles and alkyl halides, and the method also has the advantages of convenient manipulations and mild reaction conditions.

Experimental Section

General Comments. Melting points were determined on a hot-stage apparatus without correction. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ with TMS and $CDCl_3$, respectively, as the internal reference. Column chromatography was carried out on MCB silica gel (230−400 mesh). Tetrahydrofuran (THF) was freshly distilled from sodium−benzophenone. Lithiation reactions were carried out under the protection of dry nitrogen.

General Procedure for the Synthesis of Symmetrical 1,6-Diketones 5a−e. To a solution of α-benzotriazole ether **2** or **3** (5 mmol) and 1,4-dibromobutane (2 mmol) in THF (20 mL) at −78 °C was added a solution of *n*-butyllithium (4.5 mmol) in hexane. After the mixture was stirred at this temperature for 1 h, the reaction was quenched with water (5 mL). The organic phase was concentrated under vacuum. For the synthesis of **5a** and **5b,** methanol (5 mL) and 1 N hydrochloric acid (10 drops) were added, and the mixture was stirred at room temperature for 2 h. Then it was extracted with diethyl ether (3 × 30 mL), washed with saturated solutions of sodium carbonate (2 × 50 mL) and sodium chloride (50 mL), and dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography to give **5a** and **5b**. For the synthesis of **5c**,**d**, the silica gel (5 g) in dichloromethane (10 mL) containing oxalic acid (0.1 g) and water (0.1 g) was added, and the mixture was stirred at room temperature for 2 h. The workup was similar to that above.

2,13-Dimethyl-5,10-tetradecadione (**5a**): ^{1}H NMR δ 0.89 (d, 12H, J = 6.3 Hz), 1.42−1.56 (m, 10H), 2.37−2.42 (m, 8H); ^{13}C NMR δ 22.3, 23.3, 27.7, 32.6, 40.8, 42.4, 211.1. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.42; H, 12.17.

1,8-Diphenyl-2,7-octadione (**5b**):[8] ^{1}H NMR δ 1.47 (m, 4H), 2.39 (m, 4H), 3.63 (s, 4H), 7.16−7.31 (m, 10H); ^{13}C NMR δ 22.9, 41.5, 50.1, 126.9, 128.6, 129.3, 134.2, 207.8.

1,6-Diphenyl-1,6-hexadione (**5c**):[8] ^{1}H NMR δ 1.85 (m, 4H), 3.05 (m, 4H), 7.45−7.65 (m, 6H), 7.97 (d, 4H, J = 7.2 Hz); ^{13}C NMR δ 23.8, 38.3, 127.9, 128.5, 132.8, 136.9, 199.8.

1,9-Decadiene-3,8-dione (**5d**): ^{1}H NMR δ 1.65 (m, 4H), 2.63 (m, 4H), 5.83 (d, 2H, J = 10.0 Hz), 6.19−6.40 (m, 4H); ^{13}C NMR δ 23.1, 39.0, 127.8, 136.2, 200.1. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.99; H, 8.91.

1,10-Diphenyl-1,9-decadiyne-3,8-dione (**5e**): ^{1}H NMR δ 1.83 (m, 4H), 2.73 (m, 4H), 7.27−7.58 (m, 10H); ^{13}C NMR δ 23.3, 45.0, 87.7, 90.9, 119.8, 128.5, 130.7, 133.0, 187.3. Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.91; H, 6.08.

General Procedure for the Synthesis of Unsymmetrical 1,6-Diketones 8a−g. To a solution of α-benzotriazole ether **2** or **3** (20 mmol) and 1,4-dibromobutane (40 mmol) in THF (80 mL) at −78 °C was added dropwise a solution of *n*-butyllithium (21 mmol) in hexane. After the mixture was stirred at this temperature for 30 min, the reaction was quenched with water (10 mL). The organic phase was washed with a saturated solution of sodium carbonate (50 mL) and dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography to give **6** in good yield. Then to the mixture of **6** (2 mmol) and benzotriazole ether **2** or **3** (2.2 mmol) in THF (20 mL) at −78 °C was added a solution of *n*-butyllithium (2.2 mmol) in hexane. After the mixture was stirred at this temperature for 1 h, the reaction was quenched with water (5 mL). The organic phase was concentrated under vacuum. For the synthesis of **8a** and **8b,** methanol (5 mL) and 1 N hydrochloric acid (10 drops) were added, and the mixture was stirred at room temperature for 2 h. Then it was extracted with diethyl ether (2 × 30 mL), washed with saturated solutions of sodium carbonate (2 × 50 mL) and sodium chloride (50 mL), and dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography to give **8a**−**c**. For the synthesis of **8d**, **8f**, and **8g**, the silica gel (5 g) in dichloromethane (10 mL) containing oxalic acid (0.1 g) and water (0.1 g) was added, and the mixture was stirred at room temperature for 2 h. The workup was similar to that above. For the synthesis of **8e**, the silica gel (5 g) in dichloromethane (10 mL) containing oxalic acid (0.1 g) and water (0.1 g) was added, and the mixture was stirred at room temperature for 30 min. After the silica gel was filtered off, the filtrate was concentrated and treated with methanol (5 mL) and 1 N HCl (10 drops). The mixture was stirred at room temperature for 2 h. The workup was similar to that above.

11-Methyl-3,8-dodecadione (**8a**): ^{1}H NMR δ 0.89 (d, 6H, J = 6.3 Hz), 1.05 (t, 3H, J = 7.3 Hz), 1.42−1.56 (m, 7H), 2.37−2.46 (m, 8H); ^{13}C NMR δ 7.6, 22.1, 23.1, 23.2, 27.5, 32.5, 35.7, 40.7, 41.9, 42.2, 210.9, 211.1. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.71; H, 11.71.

1-Phenyl-2,7-nonadione (**8b**): ^{1}H NMR δ 1.02 (t, 3H, J = 7.3 Hz), 1.51 (m, 4H), 2.35−2.45 (m, 6H), 3.66 (s, 2H), 7.18−7.34 (m, 5H); ^{13}C NMR δ 7.6, 23.0, 23.2, 35.7, 41.4, 41.8, 50.0, 126.8, 128.5, 129.2, 134.1, 207.8, 211.0. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.54; H. 8.68. Found: C, 77.46; H, 8.96.

1-Phenyl-1,6-octadione (**8c**): ^{1}H NMR δ 1.05 (t, 3H, J = 7.3 Hz), 1.70−1.73 (m, 4H), 2.39−2.49 (m, 4H), 2.99 (t, 2H, J = 6.7 Hz), 7.43−7.58 (m, 3H), 7.95 (d, 2H, J = 7.4 Hz); ^{13}C NMR δ 7.7, 23.4, 23.7, 35.7, 38.2, 42.0, 127.8, 128.4, 132.8, 136.9, 199.7, 211.0. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.94; H, 8.50.

1-Phenyl-7-octene-1,6-dione (**8d**): ^{1}H NMR δ 1.68−1.76 (m, 4H), 2.64−2.68 (m, 2H), 2.98−3.02 (m, 2H), 5.83 (d, 1H, J = 10.2 Hz), 6.20−6.41 (m, 2H), 7.28−7.50 (m, 2H), 7.53−7.58 (m, 1H), 7.95 (d, 2H, J = 7.4 Hz); ^{13}C NMR δ 23.5, 23.7, 38.3, 39.3, 127.9, 128.0, 128.4, 128.5, 132.9, 136.5, 199.9, 200.5. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.85; H, 7.62.

1-Phenyl-1-decyne-3,8-dione (**8e**): ^{1}H NMR δ 1.05 (t, 3H, J = 7.3 Hz), 1.63−1.76 (m, 4H), 2.39−2.48 (m, 4H), 2.69 (t, 2H, J = 7.2 Hz), 7.36−7.48 (m, 3H), 7.57 (d, 2H, J = 6.9 Hz); ^{13}C NMR δ 7.7, 23.0, 23.5, 35.8, 41.8, 45.1, 87.6, 90.7, 119.8, 128.5, 130.6, 132.9, 187.4, 211.0. HRMS (CI) m/z calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1301.

1,8-Diphenyl-7-octyne-1,6-dione (**8f**): ^{1}H NMR δ 1.84 (m, 4H), 2.75 (m, 2H), 3.03 (m, 2H), 7.26−7.59 (m, 8H), 7.93−7.98 (m, 2H); ^{13}C NMR δ 23.4, 23.6, 38.1, 45.2, 87.7, 90.7, 119.9, 127.9, 128.5, 130.6, 132.9, 136.8, 187.4, 199.6. Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.61; H, 6.24.

1-Phenyl-9-decen-1-yne-3,8-dione (**8g**): ^{1}H NMR δ 1.64−1.81 (m, 4H), 2.61−2.72 (m, 4H), 5.82 (d, 1H, J = 10.3 Hz), 6.19−6.40 (m, 2H), 7.35−7.50 (m, 3H), 7.56 (d, 2H, J = 6.9 Hz); ^{13}C NMR δ 22.9, 23.3, 38.8, 44.9, 87.5, 90.4, 119.6, 127.8, 128.4, 130.5, 132.7, 136.2, 187.1, 199.9. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.60; H, 6.78.

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