JOC*Note*

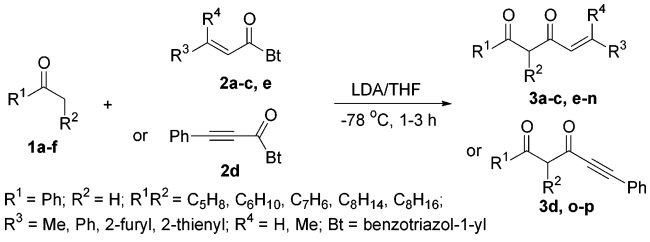
γ,δ-Unsaturated β-Diketones by Acylation of Ketones

Alan R. Katritzky,* Nabin K. Meher, and Sandeep K. Singh

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

katritzky@chem.ufl.edu

Received May 31, 2005



γ,δ-Unsaturated β-diketones have been prepared by the acylation of ketones with *N*-acylbenzotriazoles of various aliphatic and aromatic α,β-unsaturated carboxylic acids.

A number of natural products possessing medicinal activity contain γ,δ-unsaturated β-diketones, e.g., siphonarienedione[1] and cycloepiatalantin[2] (Figure 1). γ,δ-Unsaturated β-diketones are also very useful intermediates for the synthesis of 4*H*-pyran-4-ones,[3] 3-halo-4*H*-pyran-4-one pyrazoles,[4] 1-hydroxy-4-pyridones,[3] 3(2*H*)-furanones,[5] 4-pyridazinols,[6] 4*H*-thiopyran-4-thiones,[7] 5-hydroxy-2-isoxazolines,[8] substituted pyrrolo[1,2-*c*][1,2,3]-triazoles,[9] and bicyclic lactams.[10]

Acylation of ketones to give β-diketones is an important reaction for carbon−carbon bond formation.[11] Diverse methods are used for the synthesis of β-dicarbonyl compounds,[12] and those which provide γ,δ-unsaturated β-diketones from ketones include (i) acylations with α,β-unsaturated acid chlorides in the presence of sodium amide,[10,13a] pyridine,[13b] triethylamine,[13c] or LDA;[10] (ii) reaction with α,β-unsaturated esters in the presence of $Si(OMe)_4$/CsF,[14a] sodium ethoxide,[3,4,11a] or *n*-butyllithium;[14b] and (iii) aldol reactions with conjugated aldehydes to give the β-hydroxy compounds, followed by oxidation.[1,15] Another carbon acylation (iv) leading to γ,δ-unsaturated β-diketones involves the reaction of ketones with 2,2-diethoxyvinylidenetriphenylphosphorane to give stable ylides, which are treated with benzaldehyde and the resulting enol ethers are cleaved by acid (Scheme 1).[16]

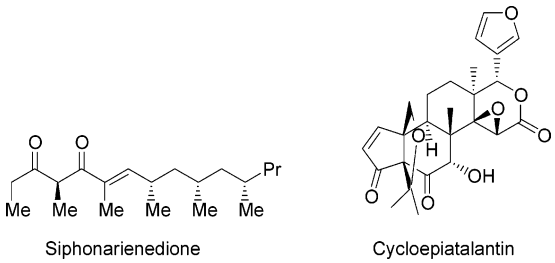


FIGURE 1. Siphonarienedione and cycloepiatalantin.

Limitations associated with the literature methods include Michael-type conjugate addition side product formation on acylation of ketones with ethyl cinnamate;[13a] cyclization leading to undesired products during Claisen condensation of acetylenic esters with ketones due to the susceptibility of the acetylenic β-diketones,[3] a requirement of hindered esters in acylation of ketones with $Si(OMe)_4$/CsF;[14a] and formation of mixtures of *O*- and *C*-acylation products.[17,11a] Moreover, acylations with acid chlorides generally suffer from their sensitivity to moisture and difficulty in handling.

N-Acylbenzotriazoles are convenient reagents for the regioselective *C*-acylation of ketones to give β-diketones.[18] We recently devised a one-pot procedure for access to unsaturated *N*-acylbenzotriazoles;[19] herein, we report their application in the acylation of ketones to give γ,δ-unsaturated β-diketones. Acylations with α,β-unsaturated acylbenzotriazoles are of particular interest since

(1) Calter, M. A.; Liao, W. *J. Am. Chem. Soc.* **2002**, *124*, 13127.
(2) Wu, T. S.; Leu, Y. L.; Chan, Y. Y.; Wu, P. L.; Kuoh, C. S.; Wu, S. J.; Wang, Y. *Phytochemistry* **1997**, *45*, 1393.
(3) El-Kholy, I. E.; Marei, M. G.; Mishrikey, M. M. *J. Heterocycl. Chem.* **1979**, *16*, 737.
(4) Marei, M. G.; Mishrikey, M. M.; El-Kholy, I. E. *J. Chem. Soc. Pak.* **1987**, *9*, 539.
(5) El-Kholy, I. E.; Mishrikey, M. M.; Marei, M. G. *J. Heterocycl. Chem.* **1982**, *19*, 1421.
(6) Marei, M. G.; Mishrikey, M. M. *Rev. Roum. Chim.* **1993**, *38*, 989.
(7) Marei, M. G. *Phosphorus Sulfur* **1993**, *81*, 101.
(8) Marei, M. G.; Ghonaim, R. A. *Indian J. Chem.* **1993**, *32B*, 418.
(9) Marei, M. G.; El-Ghanam, M.; Salem, M. M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 144.
(10) Casey, M.; Donnelly, J. A.; Ryan, J. C.; Ushioda, S. *Arkivoc* **2003**, *vii*, 310.
(11) (a) Hauser, C. R.; Swamer, F. W.; Adams, J. T. In *Organic Reactions*; Adams, R., Ed.; John Wiley & Sons: New York, 1954; Vol. 8, p 59. (b) Kel'in, A. V.; Maioli, A. *Curr. Org. Chem.* **2003**, *7*, 1855.
(12) Caine, D. In *Carbon−Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; p 250.
(13) (a) Linn, B. O.; Hauser, C. R. *J. Am. Chem. Soc.* **1956**, *78*, 6066. (b) Thakar, K. A.; Manjaramkar, N. R. *Marathwada Univ. J. Science, Sect. A* **1971**, *10*, A1. (c) Movchan, T. I.; Voloshanskii, I. S. *Zh. Prikl. Khim.* **1992**, *65*, 2393.
(14) (a) Boyer, J.; Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* **1983**, *39*, 117. (b) Hara, K.; Kashiwagi, S.; Shibuya, M. *Jpn. Kokai* **2001**, 9.
(15) Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567.
(16) Bestmann, H.-J.; Saalfrank, R. W. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 367.
(17) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514.
(18) (a) Katritzky, A. R.; Pastor, A. *J. Org. Chem.* **2000**, *65*, 3679. (b) Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617.
(19) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Synthesis* **2003**, 2795.

10.1021/jo051087f CCC: $30.25
Published on Web 08/24/2005

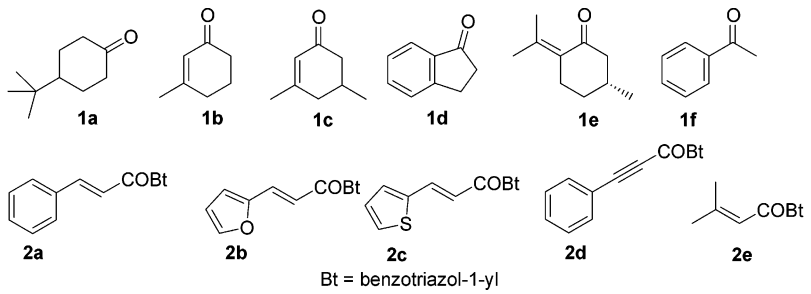
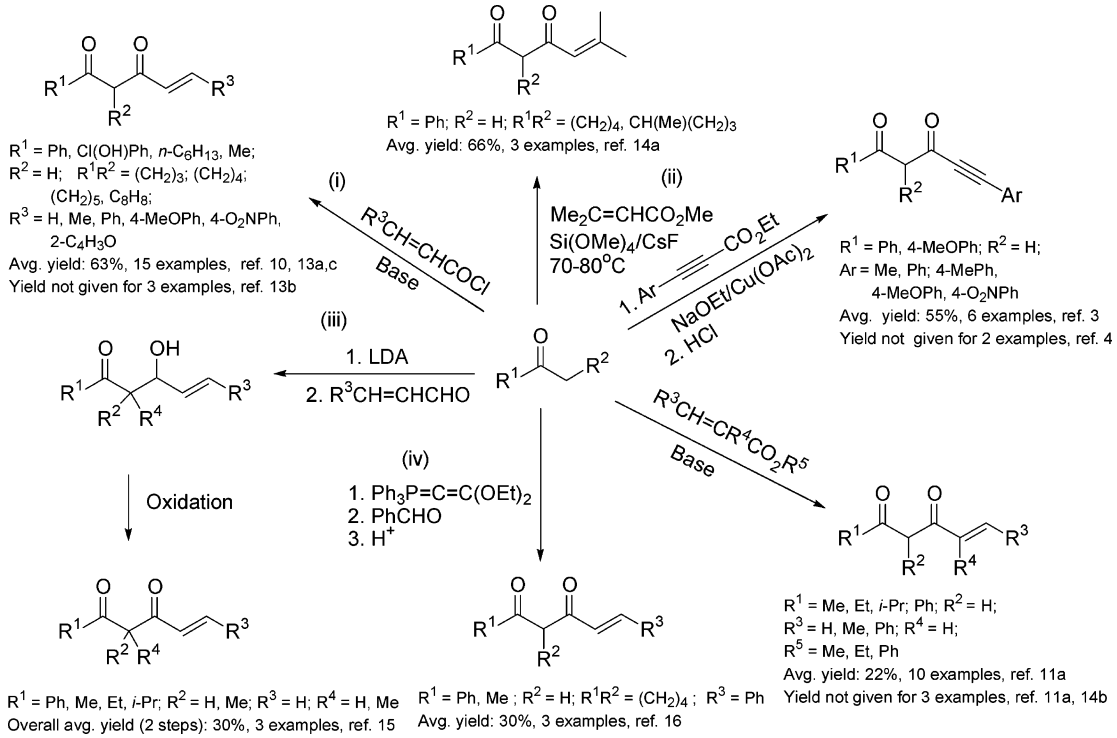


FIGURE 2. Ketones **1a**−**f** and α,β-unsaturated *N*-acylbenzotriazoles **2a**−**e**

SCHEME 1. *γ,δ*-Unsaturated *β*-Diketones from Ketones (Literature Methods)



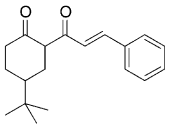
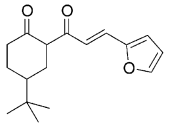
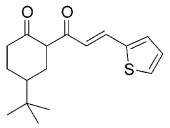
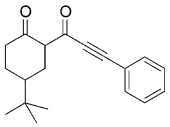
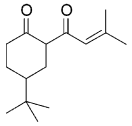
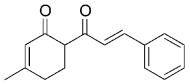
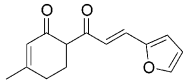
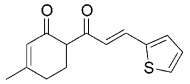
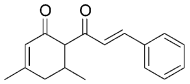
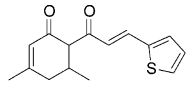
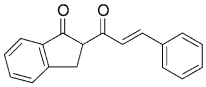
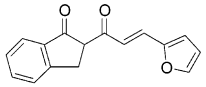
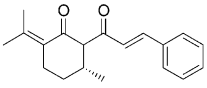
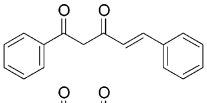
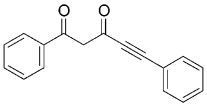
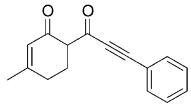
they are stable, crystalline compounds readily available from carboxylic acids and, hence, offer an effective replacement for the corresponding acid chlorides, which are usually unstable and sometimes difficult to prepare.

Preparation of Unsaturated *N*-Acylbenzotriazoles. The present work concentrated on (i) previously less studied unsaturated arylcarbonyl or heterocyclocarbonyl examples as compared to more common alkanoyl derivatives and (ii) cases where the corresponding acyl chlorides are unstable or inconvenient to prepare, for example, 2-furyl- or 2-thienyl-acryloyl derivatives. The unsaturated *N*-acylbenzotriazoles **2a**−**e** with alkyl, aryl or heterocyclic groups were prepared in 90−95% yields by the reaction of the corresponding carboxylic acids with benzotriazole and thionyl chloride at 25 °C in 2 h.[19]

Preparation of *γ,δ*-Unsaturated *β*-Diketones. A general method for the synthesis of *γ,δ*-unsaturated *β*-diketones has been developed using the ketones **1a**−**f** and α,β-unsaturated acyl benzotriazoles **2a**−**e** shown in Figure 2.

4-*tert*-Butylcyclohexanone (**1a**) on reaction with LDA at −78 °C formed the corresponding lithium enolate, which was reacted with *N*-cinnamoylbenzotriazole (**2a**) overnight to give the corresponding diketone **3a** in 62% yield (Table 1). The same result was obtained when the reaction time was reduced to 3 h. Thus, ketones such as 4-*tert*-butylcyclohexanone (**1a**), 3-methylcyclohex-2-enone (**1b**), 3,3-dimethylcyclohex-2-enone (**1c**), 1-indanone (**1d**), (*R*)-(+)-pulegone (**1e**), and acetophenone (**1f**) were acylated with a variety of aliphatic, aromatic, and heteroaromatic α,β-unsaturated acylbenzotriazoles **2a**−**e** to give the desired *γ,δ*-unsaturated *β*-diketones **3a**−**p** in 25−66% yields as colored crystalline compounds (Table 1). A slight increase in the yields of **3b** and **3p** was observed when the lithium enolate of the ketone was generated at −30 °C before addition of the *N*-acylbenzotriazole at −78 °C. All of the products (except **3n** and **3o**) are new and were fully characterized by $^{1}H/^{13}C$ NMR spectroscopy and elemental analysis. The ^{1}H NMR spectra of all products in chloroform-*d*, except **3d** and **3p**, indicate that these compounds exist in the enol form, since the anticipated hydroxy proton appears between *δ* 13.5−17.5 ppm.

TABLE 1. Acylation of Ketones 1a−f with *N*-Acylbenzotriazoles 2a−e

Entry	Ketone	RCOBt	Product	Yield (%)
1	**1a**	**2a**		**3a** (62)
2	**1a**	**2b**		**3b** (51)[a]
3	**1a**	**2c**		**3c** (62)
4	**1a**	**2d**		**3d** (30)
5	**1a**	**2e**		**3e** (38)
6	**1b**	**2a**		**3f** (44)
7	**1b**	**2b**		**3g** (52)
8	**1b**	**2c**		**3h** (42)
9	**1c**	**2a**		**3i** (45)
10	**1c**	**2c**		**3j** (42)
11	**1d**	**2a**		**3k** (53)
12	**1d**	**2b**		**3l** (40)
13	**1e**	**2a**		**3m** (51)
14	**1f**	**2a**		**3n** (66)[b]
15	**1f**	**2d**		**3o** (30)[c]
16	**1b**	**2d**		**3p** (25)[a]

[a] Generation of lithium enolate at −30 °C for 30 min followed by the addition of acylating agent at −78 °C, 1 h. [b] Previously prepared by acid chloride/sodioketone (2 equiv) in 77% yield. [c] Previously prepared by sodium ethoxide/ester in 50−60% yields.

Compounds (**3a**−**c**,**f**−**n**) where there is a possibility of geometrical isomerism are in the *E*-form as evidenced from the coupling constants (J = 15.0−16.0 Hz) between protons attached to the carbon−carbon double bond. The formation of product was also evident by comparison of the ^{1}H NMR data with that of the starting ketone, for example, **1a** showed four signals but after acylation with **2a**, the product **3a** showed six signals due to aliphatic protons and one signal due to the enolic proton appearing at δ 16.80 ppm. The IR spectrum of **3a** shows a peak at 1627 cm^{-1} due to the carbonyl group.

A general method for the preparation of γ,δ-unsaturated β-diketones from the corresponding mono ketones by acylation with *N*-(α,β-unsaturated acyl)benzotriazoles has been developed. Features of this method compared to preexisting methodology include the following: (i) stable and easily accessible acylating agents are used; (ii) reactions proceed at −78 to −30 °C compared with −78 to 80 °C; (iii) reaction times are 1−3 h as compared with up to 24 h; (iv) average yields are 46% compared with an average yield of 44% as given in Scheme 1.

Experimental Section

4-*tert*-Butyl-2-[(*E*)-3-phenyl-2-propenoyl]cyclohexanone (3a): yield 0.36 g (62%); yellow needles (from hexane); mp 128−130 °C; ^{1}H NMR δ 0.97 (s, 9H), 1.30−1.42 (m, 2H), 1.89−1.95 (m, 1H), 2.17−2.25 (m, 1H), 2.41−2.55 (m, 2H), 2.61−2.67 (m, 1H), 6.96 (d, J = 15.6 Hz, 1H), 7.38−7.40 (m, 3H), 7.56−7.59 (m, 2H), 7.72 (d, J = 15.6 Hz, 1H), 16.80 (s, 1H); ^{13}C NMR δ 23.1, 25.3, 27.6, 32.7, 35.1, 44.9, 107.2, 119.9, 128.4, 129.1, 130.2, 135.6, 141.6, 180.9, 193.6. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.29; H, 8.71.

4-*tert*-Butyl-2-[(*E*)-3-(2-thienyl)-2-propenoyl]cyclohexanone (3c): yield 0.36 g (62%); orange needles (from hexane); mp 93−94 °C; ^{1}H NMR δ 0.97 (s, 9H), 1.30−1.37 (m, 2H), 1.89−1.92 (m, 1H), 2.13−2.22 (m, 1H), 2.40−2.61 (m, 3H), 6.73 (d, J = 15.3 Hz, 1H), 7.05−7.08 (m, 1H), 7.26−7.28 (m, 1H), 7.37 (d, J = 5.1 Hz, 1H), 7.82 (d, J = 15.0 Hz, 1H), 16.79 (s, 1H); ^{13}C NMR δ 23.1, 25.2, 27.6, 32.7, 35.0, 44.9, 103.6, 107.1, 118.9, 128.5, 131.1, 134.2, 141.1, 180.9, 193.0. Anal. Calcd for $C_{17}H_{22}O_2S$: C, 70.31; H, 7.64. Found: C, 70.26; H, 7.70.

4-*tert*-Butyl-2-(3-phenyl-2-propynoyl)cyclohexanone (3d): yield 0.17 g (30%); colorless needles (from hexane/EtOAc); mp 145−146 °C; ^{1}H NMR δ 0.95 (s, 9H), 1.37−1.49 (m, 2H), 1.92−2.01 (m, 1H), 2.11−2.15 (m, 1H), 2.44−2.50 (m, 1H), 2.60−2.68 (m, 2H), 6.72 (s, 1H), 7.36−7.44 (m, 3H), 7.79−7.81 (m, 2H); ^{13}C NMR δ 19.8, 23.6, 25.8, 27.5, 32.6, 44.3, 112.0, 115.6, 128.9, 129.8, 131.5, 132.4, 147.0, 180.0, 187.3. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.90; H, 8.20.

1,5-Diphenyl-4-pentyne-1,3-dione (3o): yield 0.15 g (30%); pale yellow needles (from hexane/EtOAc); mp 94 °C (lit.[3] mp 95 °C); ^{1}H NMR δ 6.53 (s, 1H), 7.36−7.50 (m, 5H), 7.54−7.61 (m, 3H), 7.92−7.95 (m, 2H), 15.80 (s, 1H); ^{13}C NMR δ 86.3, 94.1, 101.5, 120.6, 127.5, 128.8, 129.0, 130.6, 132.9, 133.2, 134.7, 170.6, 185.5. Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 81.93; H, 4.79.

Supporting Information Available: General experimental details for the preparation of unsaturated *N*-acylbenzotriazoles **2a**−**e** and for acylation with unsaturated *N*-acylbenzotriazoles and characterization data for compounds **2a**−**e** and **3b**,**e**−**n**,**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051087F