JOC Article

Preparation of β-Keto Esters and β-Diketones by C-Acylation/Deacetylation of Acetoacetic Esters and Acetonyl Ketones with 1-Acylbenzotriazoles

Alan R. Katritzky,* Zuoquan Wang, Mingyi Wang, Chavon R. Wilkerson, C. Dennis Hall, and Novruz G. Akhmedov

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

katritzky@chem.ufl.edu

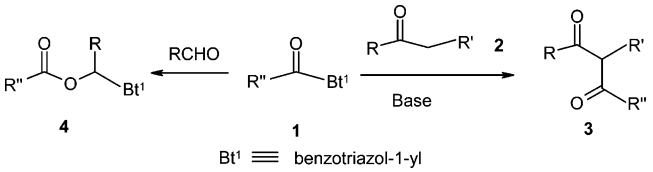
Received April 29, 2004

Acyl-, aroyl-, and heteroaroyl-acetic esters **6a**−**f** and **8a**−**l** are prepared by reactions of 1-acylbenzotriazoles **1a**−**k** with acetoacetic esters **5** or **7a**,**b** in the presence of sodium hydride followed by regioselective deacetylation. Similar C-acylation/deacetylation of acetylacetone and benzoylacetone affords β-diketones **10a**−**d** and **13a**−**c**, respectively.

Introduction

β-Keto esters and β-diketones have been important intermediates in organic synthesis since the discovery of the Claisen condensation more than a century ago.[1a−i] Familiar general syntheses of β-diketones and β-keto esters include (i) acylation of ketones or carboxylic esters by acyl halides or esters[2a−d] and (ii) acylation of acetylacetone or ethyl acetoacetate and their substituted derivatives by acyl halides or esters followed by base-promoted cleavage of a carbonyl group.[3a−c] The above methods offer many useful synthetic procedures, but some acyl halides, such as 3-phenyl-2-propynoyl chloride and 2-pyridoyl chloride, are quite tedious to synthesize, store, and handle and therefore are often prepared in situ. Moreover, β-keto ester and β-diketone anions are ambident; thus, when acetylacetone or ethyl acetoacetate are reacted with electrophiles such as acyl chlorides in the presence of base, both C- and/or O-acylation can occur. For example, under phase-transfer conditions, acylation of acetylacetone and of ethyl acetoacetate with acetyl chloride and benzoyl chloride yielded O-acylated enol esters in 83−98% yields.[4a−c] The nature of the solvent, electrophile, metal counterion, reaction temperature, and structure of the substrate influence the chemoselectivity of such acylations.[5]

SCHEME 1



Benzotriazole is a good leaving group and has been used extensively as a novel synthetic auxiliary.[6a−c] Generally, 1-acylbenzotriazoles **1** are more stable than acid chlorides and can be used in many N-,[7a−d] C-,[8a−c] and O-acylation reactions[9a,b] (Scheme 1).

We now show that C-acylations of acetoacetic esters by 1-acylbenzotriazoles, followed by spontaneous deacetylation, lead to useful preparative methods for acyl-, aroyl-,

* Corresponding author.

(1) (a) Claisen, L.; Lowman, O. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 651−654. (b) Claisen, L. *Liebigs Ann. Chem.* **1896**, *291*, 100−111. (c) Yoshida, M.; Fujikawa, K.; Sato, S.; Hara, S. *Arkivoc* **2003**, *vi*, 36−42. (d) Cristau, H.-J.; Marat, X.; Vors, J.-P.; Pirat, J.-L. *Tetrahedron Lett.* **2003**, *44*, 3179−3181. (e) Christoffers J.; Oertling, H.; Fisher, P.; Frey, W. *Tetrahedron* **2003**, *59*, 3769−2778. (f) Kotha, S.; Manivannan, E. *Arkivoc* **2003**, *iii*, 67−76. (g) Kollenz, G.; Dalvi, T. S.; Kappe, C. O.; Wentrup, C. *Arkivoc* **2000**, *1* (1), 74−79. (h) Katritzky, A. R.; Silina, A.; Tymoshenko, D. O.; Qiu, G.; Nair, S. K.; Steel, P. J. *Arkivoc* **2001**, *vii*, 138−144. (i) Falsone, F. S.; Kappe, C. O. *Arkivoc* **2001**, *ii*, 122−134.

(2) (a) Movchan, T. I.; Voloshanovskii, I. S. *J. Appl. Chem. USSR (Engl. Transl.)* **1992**, *65*, 1973−1976. (b) Linn, B. O.; Hauser, C. R. *J. Am. Chem. Soc.* **1956**, *78*, 6066−6070. (c) Hauser, C. R.; Hudson, B. E., Jr. In *Org. React.*; Adams, R., Bachmann, W. E., Johnson, J. R., Fieser, L. F., Snyder, H. R., Eds.; John Wiley & Sons: New York, 1942; Vol. 1, pp 266−289. (d) Casey, M.; Donnelly, J. A.; Ryan, J. C.; Ushioda, S. *Arkivoc* **2003**, *vii*, 310−327.

(3) (a) Berend, L.; Heymann, F. *J. Prakt. Chem.* **1902**, 290−294. (b) Duff, J. C. *J. Chem. Soc.* **1914**, *105*, 2182−2186. (c) McElvain, S. M.; Weber, K. H. *J. Am. Chem. Soc.* **1941**, *63*, 2192−2197.

(4) (a) March, J. *March's Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1985; pp 436−436. (b) Jones, R. A.; Nokkeo, S.; Singh, S. *Synth. Commun.* **1977**, *7*, 195−199. (c) Taylor, E. C.; Hawks, G. H., III; Mckillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2421−2422.

(5) Black, T. H. *Org. Prep. Proced. Int.* **1989**, *21*, 179−217.

(6) (a) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683−2732. (b) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409−548. (c) Katritzky, A. R.; Lan, X.; Fan, W.-Q. *Synthesis* **1994**, 445−456.

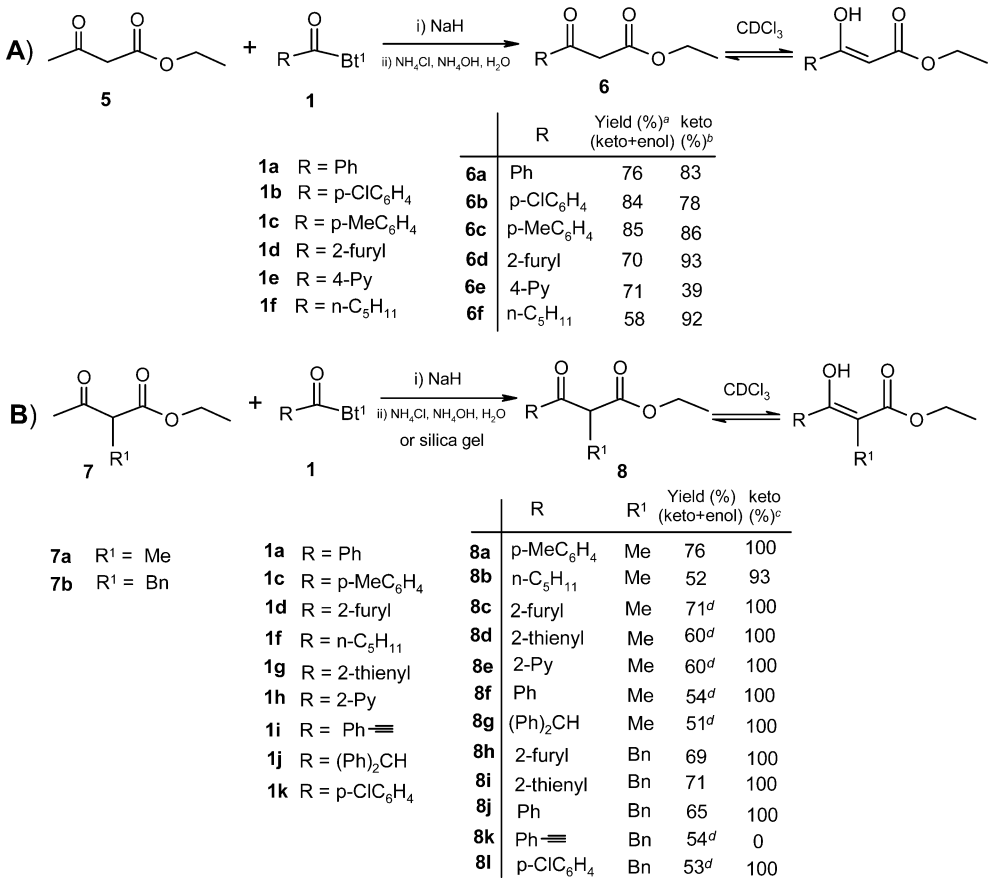
(7) (a) Katritzky, A. R.; Levell, J. R.; Pleynet D. P. M. *Synthesis* **1998**, 153−156. (b) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210−8213. (c) Katritzky, A. R.; Wang, M.; Yang, H.; Zhang, S.; Akhmedov, N. G. *Arkivoc* **2002**, *viii*, 134−142. (d) Katritzky, A. R.; Rogovoy, B. V.; Kirichenko, N.; Vvedensky, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1809−1811.

(8) (a) Katritzky, A. R.; Pastor, A.; *J. Org. Chem.* **2000**, *65*, 3679−3682. (b) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 1443−1446. (c) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 4932−4934.

(9) (a) Katritzky, A. R.; Pastor, A.; Voronkov, M. V. *J. Heterocycl. Chem.* **1999**, *36*, 777−781. (b) Wedler, C.; Kleiner, K.; Kunath, A.; Schick, H. *Liebigs Ann.* **1996**, 881−885.

10.1021/jo049274l CCC: $27.50
Published on Web 08/26/2004

SCHEME 2



	R	Yield (%)[a] (keto+enol)	keto (%)[b]
6a	Ph	76	83
6b	p-ClC_6H_4	84	78
6c	p-MeC_6H_4	85	86
6d	2-furyl	70	93
6e	4-Py	71	39
6f	n-C_5H_{11}	58	92

	R	R^1	Yield (%) (keto+enol)	keto (%)[c]
8a	p-MeC_6H_4	Me	76	100
8b	n-C_5H_{11}	Me	52	93
8c	2-furyl	Me	71[d]	100
8d	2-thienyl	Me	60[d]	100
8e	2-Py	Me	60[d]	100
8f	Ph	Me	54[d]	100
8g	$(Ph)_2CH$	Me	51[d]	100
8h	2-furyl	Bn	69	100
8i	2-thienyl	Bn	71	100
8j	Ph	Bn	65	100
8k	Ph≡	Bn	54[d]	0
8l	p-ClC_6H_4	Bn	53[d]	100

[a] Products were recovered as mixtures of keto/enol tautomers as evidenced by ^{1}H NMR in $CDCl_3$. [b] Determined by ^{1}H NMR of products **6**. [c] Products were recovered almost entirely in keto form with the exception of **8b** and **8k**, where the percentage of the enol form was 7% for **8b** and 100% for **8k** as determined by ^{1}H NMR in $CDCl_3$. [d] Quenched with silica gel.

and heteroaroyl-acetic esters. Similar treatment of acetonyl ketones affords a variety of *β*-diketones.

Results and Discussion

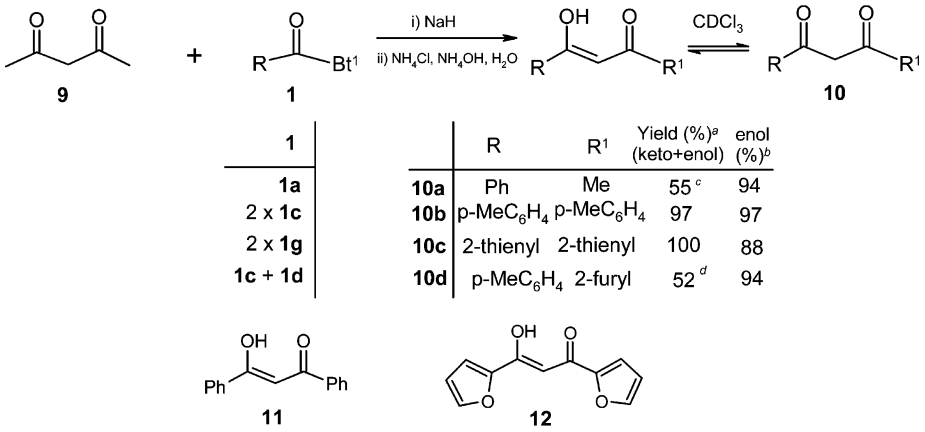
1-Acylbenzotriazoles **1a**−**n** were readily prepared by treating carboxylic acids either (i) in THF with 1-(methylsulfonyl)-1*H*-1,2,3-benzotriazole in the presence of triethylamine under reflux overnight[7b]or (ii) with thionyl chloride and benzotriazole at 25 °C.[10]

Condensation of the corresponding enolates of ethyl acetoacetate **5** (Scheme 2, A) with 1-acylbenzotriazoles **1a**−**f** at rt for 14 h, followed by cleavage of the acetyl group in situ with an aqueous solution of ammonium chloride and ammonium hydroxide under reflux and in the presence of benzotriazole moiety gave *β*-keto esters **6a**−**f** in 58−85% yields. No O-acylation or other byproducts were detected.

The structures of the known *β*-keto esters **6a**,[11] **6b**,[12] **6c**,[13] **6d**,[14] **6e**,[15] and **6f**[6] are supported by comparison of their melting points and spectroscopic data with literature reports and, in some cases, by ^{1}H/^{13}C NMR data together with microanalyses. The ^{1}H NMR spectra of **6a**−**f** show new sets of singlets at *δ* 3.43−4.86 assigned to the α-methylene protons, and the ^{13}C NMR spectra show signals at *δ* 45.3−49.2 corresponding to the α-methylene carbons. While some ^{1}H and ^{13}C signals for enol forms in the tautomeric mixtures **6a**−**f** are not visible or overlap with those of their keto forms, singlets at *δ* 4.98−6.61 in ^{1}H NMR spectra and signals at *δ* 86.6−89.9 in ^{13}C NMR spectra are assigned to the olefinic hydrogens and their respective carbons and clearly indicate the presence and relative quantity of the corresponding enol forms. An exception is **6d**, for which the ^{13}C signal of the α-methine carbon was not observed. In nearly all cases, the keto forms of the *β*-keto esters **6** predominate in the keto−enol tautomeric mixtures in $CDCl_3$ solution. An exception, however, is **6e**, where at 20 °C in $CDCl_3$ solution the enol:keto ratio is 3:2, probably due to the strong electron-withdrawing effect of the pyridyl group (Scheme 2,A). This assignment and tautomeric preference

(10) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Synthesis* **2003**, 2795−2798.
(11) Balaji, B. S.; Chanda, B. M. *Tetrahedron* **1998**, *54*, 13237−13252.
(12) Lee, L. F.; Schleppnik, F. M.; Howe, R. K. *J. Heterocycl. Chem.* **1985**, *22*, 1621−1630.
(13) Karnik, A. V.; Rane, J. P. *Indian J. Chem. Sect. B* **1998**, *37*, 1191−1193.
(14) Taylor, E. C.; Turchi, I. J. *Org. Prep. Proced. Int.* **1978**, *10*, 221−224.
(15) Carabateas, P. M.; Brundage, R. P.; Gelotte, K. O.; Gruett, M. D.; Lorenz, R. R.; Opalka, C. J., Jr.; Singh, B.; Thielking, W. H.; Williams, G. L.; Lesher, G. Y. *J. Heterocycl. Chem.* **1984**, *21*, 1849−1856.
(16) Matsuo, K.; Kimura, M.; Kimuta, T.; Takai, N.; Tanata, K. *Chem. Parm. Bull.* **1984**, *32*, 4197−4204.

SCHEME 3



1		R	R¹	Yield (%)[a] (keto+enol)	enol (%)[b]
1a	10a	Ph	Me	55[c]	94
2 x 1c	10b	p-MeC$_6$H$_4$	p-MeC$_6$H$_4$	97	97
2 x 1g	10c	2-thienyl	2-thienyl	100	88
1c + 1d	10d	p-MeC$_6$H$_4$	2-furyl	52[d]	94

[a] Products were recovered in mixtures of enol/keto tautomers as evidenced by ^{1}H NMR in $CDCl_3$. [b] Determined by ^{1}H NMR of products **10a**−**d**. [c] Byproduct **11** was isolated in 18% yield. [d] Byproducts **10b** and **12** were isolated in 23 and 24% yields, respectively.

is in accord with the results of previously reported theoretical and experimental studies.[17]

Transformations analogous to those described above also succeeded with other α-acetyl carboxylic esters. Thus, β-keto esters **7a** and **7b** were similarly converted into **8a**−**g** and **8h**−**k**, respectively in 51−76% isolated yields (Scheme 2B).

The keto structures of the known **8a**,[18] **8c**,[19] **8f**,[20] **8j**,[21] and novel **8b**,**d**,**e**,**g**−**i**,**l** are confirmed by their ^{1}H/^{13}C NMR data. The ^{1}H NMR spectra for each of **8a**−**g** show two sets of quartets between δ 3.51 and 4.71 assigned to α-methine protons and OCH_2 protons and for **8h**−**j**,**l** triplets between δ 4.41 and 4.62 corresponding to α-methine protons. The ^{13}C NMR signals for **8a**−**j**,**l** at δ 47.3−57.4 correspond to tertiary carbons of the keto forms. The only enol form detected as a minor tautomer among **8a**−**j**,**l** was in **8b** (7% enol in $CDCl_3$ solution), for which δ_H = 12.80 (OH) and δ_C = 94.6 (the disubstituted olefinic carbon) were found. Unlike **8a**−**j**,**l** ethyl (*Z*)-2-benzyl-3-hydroxy-5-phenyl-2-penten-4-ynoate **8k** exists entirely in the enol form in $CDCl_3$ solution. Thus, the ^{1}H NMR spectrum of **8k** shows two singlets at δ 3.80 and 12.40, corresponding to the two methylene protons in the benzyl group and hydroxy group in the enol form, respectively, and ^{13}C NMR shows a signal at δ 108.4, assigned to the disubstituted olefinic carbon. This assignment is in accord with previously reported experimental studies.[22]

Analogous transformations also worked smoothly with acetylacetone **9** (Scheme 3). Thus, reaction of **9** with **1a** produced both the expected β-diketone **10a** (55%) predominately in the enol form (in $CDCl_3$) and dibenzoylmethane **11**[23] (18%) as a byproduct of a double reaction in which both acetyl groups were replaced by benzoyl. Reaction of **9** with 2 equiv of either **1c** or **1g** gave symmetrical β-diketones **10b** and **10c** in almost quantitative yields. Reaction of **9** with a mixture of 1 equiv of **1c** and 1 equiv of **1d** yielded unsymmetrical β-diketone **10d** in 52% yield and two byproducts **10b** and **12**[24] in 23 and 24% yields, respectively.

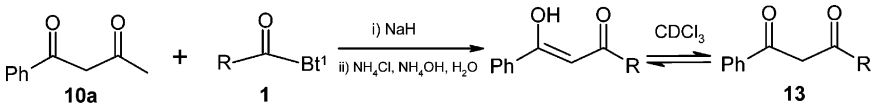
The enol structures of the known β-diketones **10a**,[25a,b] **10b**,[26] and **10c**[27] and the novel **10d** are supported by ^{1}H/^{13}C NMR spectra, which show a set of singlets at δ 6.18−6.81 corresponding to the α-olefinic protons and signals at δ 92.1−96.7 assigned to the α-olefinic carbons.[28] All the β-diketones **10a**−**d** contained the corresponding keto forms as minor tautomers. The minor keto structures were characterized by ^{1}H singlets between δ 4.1 and 4.57 and ^{13}C NMR signals between δ 50 and 54.7, and the relative amounts were estimated by ^{1}H NMR.

An analogous transformation was successful with 1-benzoylacetone **10a** which, on reaction with 1-acylbenzotriazole **1l** produced the expected β-diketone **13a** in 62% yield almost entirely in the enol form. Reaction with **1d** gave **13b** in 61% yield and two byproducts **11** and **12** in 17 and 15% yields, respectively. Similarly, reaction with **1g** produced **13c** (61%) (Scheme 4).

The structures of the known products **13a**,[29] **13b**,[30] and **13c**[31a,b] are supported by microanalyses and ^{1}H/^{13}C NMR data, which show ^{1}H singlets between δ 6.37 and 6.77 and ^{13}C signals at δ 92.7−96.2 corresponding to enol forms.[28] Compounds **13a** and **13b** contained the corre-

(17) Burdett, J. L.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 2105−2109.
(18) Emelina, E. E.; Semenova, N. A.; Ershov, B. A. *J. Org. Chem. USSR (Engl. Transl.)* **1974**, *10*, 1044−1048.
(19) Lukeš, R.; Šrogl, J. *Collection Czechoslov. Chem. Commun.* **1961**, *26*, 2238−2243.
(20) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229−4235.
(21) Queignec, R.; Kirschleger, B.; Lambert, F.; Aboutaj, M. *Synth. Commun.* **1988**, *18*, 1213−1223.
(22) Zaugg, H. E.; Michaels, R. J.; Baker, E. J. *J. Am. Chem. Soc.* **1968**, *90*, 3800−3808.
(23) Allen, C. F. H.; Abell, R. D.; Normington, J. B. In *Organic Syntheses*; Gilman, H., Adams, R., Marvel, C. S., Clarke, H. T., Noller, C. R., Conant, J. B., Whitmore, F. C., Eds.; John Wiley & Sons: New York, 1941; Coll. Vol. 1, pp 205−206.
(24) Barluenga, J.; del Pozo, C.; Olano, B. *Synthesis* **1996**, 133−140.
(25) (a) Ukai, K.; Oshima, K.; Matsubara, S. *J. Am. Chem. Soc.* **2000**, *122*, 12047−12048. (b) Muir, W. M.; Ritchie, P. D.; Lyman, D. J. *J. Org. Chem.* **1966**, *31*, 3790−3793.
(26) Hao, W.; Zhang, Y.; Ying, T.; Lu, P. *Synth. Commun.* **1996**, *26*, 2421−2427.
(27) Ishii, A.; Nakuyama, J.; Kazami, J.-i.; Ida, Y.; Nakamura, T.; Hoshino, M. *J. Org. Chem.* **1991**, *56*, 78−82.
(28) Hayamizu, K.; Yanagisawa, M.; Yamamoto, O. *Japanese Integrated Spectral Data Base System for Organic Compounds*; National Institute of Advanced Industrial Science and Technology: Tsukuba, Japan, 2001; SDBS No. 874.
(29) Tolkunov, S. V. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1998**, *34*, 1132−1136.
(30) Okuzumi, T. *Nippon Kagaku Zasshi* **1961**, *82*, 1235−1240.
(31) (a) Mitchell, A. D.; Nonhebel, D. C. *Tetrahedron* **1976**, *32*, 2437−2438. (b) Harris, S. R.; Levine, R. *J. Am. Chem. Soc.* **1948**, *70*, 3360−3361.

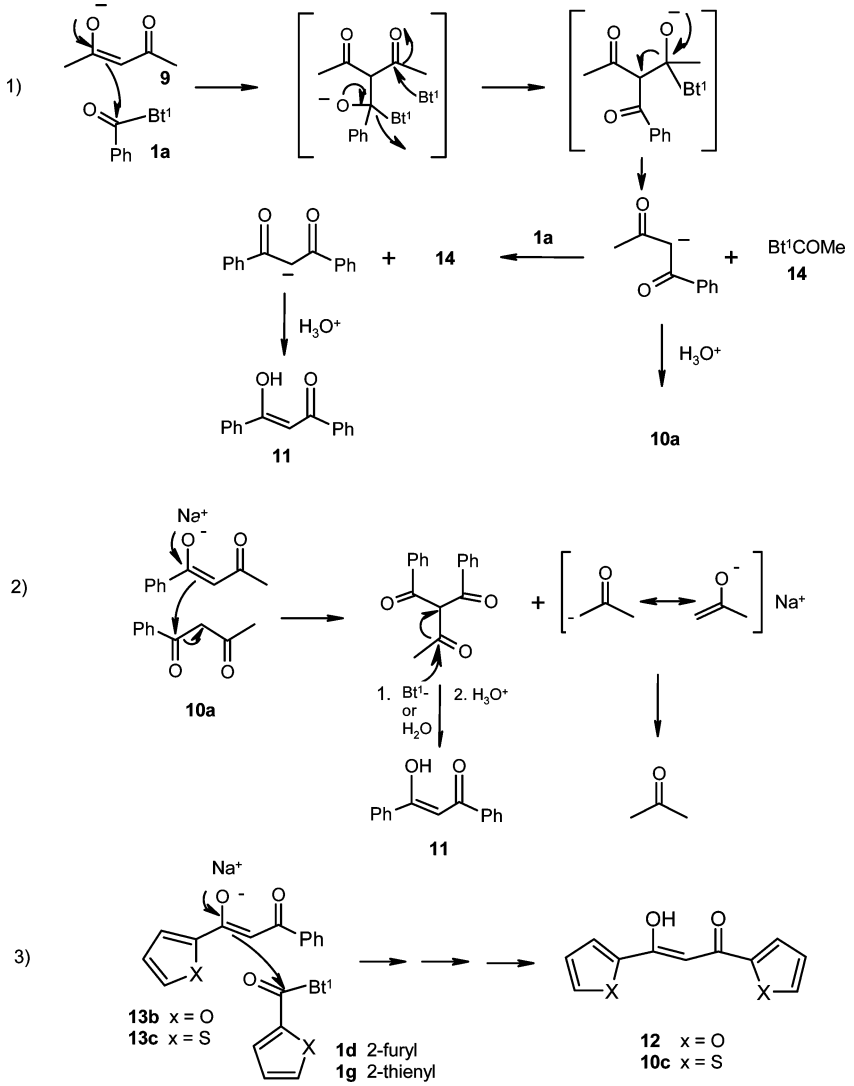
SCHEME 4



			R	Yield (%)[a] enol	(keto+enol) (%)[b]
1k	R = $PhSCH_2$	**13a**	$PhSCH_2$	62	93
1d	R = 2-furyl	**13b**	2-furyl	61[c]	97
1g	R = 2-thienyl	**13c**	2-thienyl	61[d]	100

[a] Products were recovered in mixtures of enol/keto tautomers as evidenced by ^{1}H NMR in $CDCl_3$. [b] Determined by ^{1}H NMR of products **13a**−**c**. [c] Byproducts **11** and **12** were isolated in 17 and 15% yields respectively. [d] Byproducts **11** and **10c** were isolated in 16 and 15% yields, respectively.

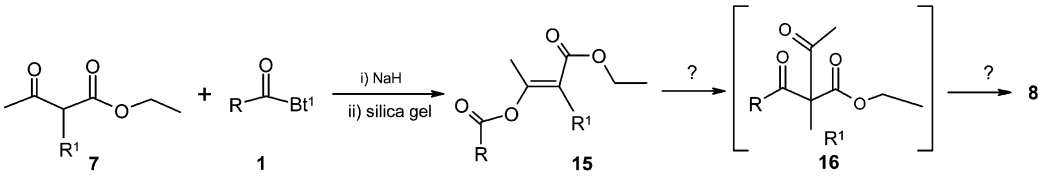
SCHEME 5



sponding keto forms as the minor tautomers in $CDCl_3$ solution, but no keto form was detected in **13c**. The keto structures of **13a** and **13b** were characterized by ^{1}H singlets between δ 4.28 and 4.48 and ^{13}C signals between δ 51 and 50.0.

When the reaction of **9** with **1a** was quenched with dilute hydrochloric acid, **10a** (57%) and **11** (16%) were again obtained in yields similar to those showed in Scheme 3, together with 1-(1*H*-1,2,3-benzotriazol-1-yl)-1-ethanone **14**[9a] (21%, Scheme 5), but no 1-(2*H*-1,2,3-benzotriazol-2-yl)-1-ethanone was detected. Formation and isolation of 1-(1*H*-1,2,3-benzotriazol-1-yl)-1-ethanone **14** suggests an intermolecular benzotriazole-mediated acylation/deacetylation process to give **10a**, **11**, and **14**, which is similar to one previously reported[13] (path 1 of Scheme 5). Presumably, formation of **11** in reactions of **10a** with **1d** or **1g** (Scheme 4) followed path 2 of Scheme 5 and formation of **12** and **10c** followed path 3 of Scheme

SCHEME 6



7a R^1 = Me
7b R^1 = Bn

1m R = Ph-cyc-C_3H_4[a]
1n R = 2-PhEtPh[b]
1a R = Ph
1c R = p-MeC_6H_4

	R	R	T (h)	Yield (%)
15a	Ph-cyc-C_3H_4[a]	Me	2	28
15b	2-PhEtPh[b]	Me	3	27
15c	Ph	Bn	3.5	31
15d	p-MeC_6H_4	Bn	3.5	31
15e	Ph-cyc-C_3H_4[a]	Bn	3.5	36

[a] 1-Phenylcyclopropyl. [b] 2-(2-Phenylethyl)phenyl.

5. In these cases, however, debenzoylation took place, instead of deacetylation.

Attempts to capture the postulated C-acylated intermediates **16** (Scheme 6) by shortening the reaction time to 2−3.5 h and avoiding the hydrolysis step by quenching with silica gel failed. Under these conditions, the main isolated intermediates were O-acylated (*E*)-enol esters **15a**−**e** in 27−36% yields.

A possible explanation for the formation of **15a**−**e**, but not the C-acylated intermediates **16**, is that formation of the O-acylated (*E*)-enol esters is less sterically hindered than formation of C-acylated intermediates. This is supported by formation of C-acylated products **8c**−**g** and **8k**,**l**, which have relatively small acyl groups when the reactions were also quenched with silica gel (Scheme 2B). Presumably, in some cases, e.g., (*E*)-enol ester **15c** and keto ester **8j**, kinetically favored O-acylation products **15** gradually convert to their corresponding C-acylation intermediates **16**, which in the presence of benzotriazole moiety form the thermodynamically stable C-acylation products **8**. Similarly, during the preparation of keto ester **8l**, the corresponding O-acylation product **15** was isolated and characterized by ^{1}H NMR with a reaction time of 3 h; however, with a reaction time of 14 h, only **8l** was isolated.

The spectral and analytical data of the novel **15a**−**e** confirm their (*E*)-enol ester structures. Thus, ^{1}H NMR for **15a**,**b** show typical homoallylic coupling constants of 1.5 Hz for two olefinic methyl groups. Each ^{1}H NMR spectrum of the remaining three enol esters **15c**−**e** displays a triplet between δ 2.29 and 2.46 and a slightly broadened singlet between δ 3.48 and 3.66 corresponding to the olefinic methyl and the methylene of benzyl groups, respectively. The (*E*)-configuration of **15a**−**e** is supported by the fact that no NOE enhancement was found between the two olefinic methyl groups of **15a**,**b** or the methyl and the benzyl groups of **15c**−**e**. Olefinic carbons were also detected in the ^{13}C spectra of **15a**−**e** at δ 117.0−121.8 and 156.7−157.6, consistent with previously reported experimental studies[32]

In summary, a simple procedure for the preparation of acetoacetic esters and α-acetyl ketones has been developed by treatment of starting acetoacetic esters or α-acetyl ketones with 1-acylbenzotriazoles in the presence of sodium hydride, followed by hydrolysis. The advantage of this method includes the following: (i) most acylbenzotriazoles are stable to storage over months; (ii) the use of acylbenzotriazoles offers mild reaction conditions and operational ease and, more importantly, O-acylation is greatly reduced; and (iii) acetoacetic esters and α-acetyl ketones are obtained in good to excellent yields. The approach offers efficient, one-pot methodology for functional group interchange by acylation, aroylation, or heteroaroylation of α-acetyl ketones or acetoacetic esters followed by deacetylation. The method is probably most valuable when it is desirable to avoid using the corresponding acid chlorides.

(32) Zhao, L.; Lu, X. *Org. Lett.* **2002**, *4*, 3903−3906.

Experimental Section

General Methods and Materials. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard for ^{1}H (300 MHz) or $CDCl_3$ as the internal standard for ^{13}C (75 MHz), unless otherwise specified. Elemental and mass spectrometry analyses were performed by Analytical Laboratories, Department of Chemistry, University of Florida. All reactions were carried out under an atmosphere of nitrogen. Anhydrous THF was obtained by distillation immediately prior to use, from sodium/benzophenone ketyl. Column chromatography was performed with S733-1 silica gel (200−425 mesh).

General Procedure for the Preparation of *β*-Keto Esters 6a−f. To a stirred solution of ethyl acetoacetate **5** (0.66 g, 5 mmol) in THF (30 mL) was added NaH (60%, 0.27 g, 5.5 mmol) at rt, and stirring was continued for 40 min under nitrogen. Each 1-acylbenzotriazole (**1a**−**f**: 5 mmol) in THF (30 mL) was then added by syringe at room temperature, and the resulting mixture was stirred at room temperature for 14 h under nitrogen. Water (22 mL), ammonium chloride (0.88 g, 16.5 mmol), and ammonium hydroxide (28.8%, 0.21 mL) were added to the mixture, which was then heated under reflux for 1 h. The mixture was acidified to pH 5 with 0.05 N HCl (∼50 mL) and then extracted with AcOEt (3 × 50 mL). The combined organic phase was washed with water (2 × 50 mL) and dried over anhydrous $MgSO_4$. Removal of solvents under reduced pressure and purification of the residue by column chromatography on silica gel gave the corresponding pure *β*-keto esters **6**.

General Procedure for the Preparation of α-Monoalkyl-Substituted *β*-Keto Esters 8a,b,h−j. To a stirred solution of ethyl α-monosubstituted acetoacetate **7a** or **7b** (5 mmol) in THF (30 mL) was added NaH (60%, 0.20 g, 5 mmol for **8a**,**b**,**h**,**i**; 0.27 g, 6.6 mmol for **8j**) at room temperature, and stirring was continued for 40 min under nitrogen. Each 1-acylbenzotriazole (**1c**,**f**,**d**,**g**,**a**: 5 mmol) in THF (30 mL) was added by syringe at room temperature, and the resulting mixture was stirred for

14 h under nitrogen. Water (22 mL), ammonium chloride (0.88 g, 16.5 mmol), and ammonium hydroxide (28.8%, 0.21 mL) were added to the mixture, which was then heated under reflux for 1 h. The mixture was worked up in the same method as for **6** to give the corresponding pure *β*-keto ester **8**.

General Procedure for the Preparation of α-Monoalkyl-Substituted *β*-Keto Esters 8c−g,l and α-Benzyl-*β*-enol Ester 8k. To a stirred solution of ethyl α-monosubstituted acetoacetate **7a** or **7b** (5 mmol) in THF (30 mL) was added NaH (60%, 0.20 g, 5 mmol) at room temperature, and stirring was continued for 40 min under nitrogen. Each 1-acylbenzotriazole (**1d**,**g**,**h**,**a**,**j**,**i**,**k**: 5 mmol) in THF (30 mL) was added by syringe at room temperature, and the resulting mixture was stirred for 3−14 h. A small amount of silica gel was added to the reaction mixture and THF was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding α-monoalkyl-substituted *β*-keto esters **8c**−**g**,**l** and α-benzyl-*β*-enol ester **8k**.

General Procedure for the Preparation of *β*-Diketones 10a−d. To a stirred solution of the acetylacetone **9** (0.51 g, 5 mmol) in THF (30 mL) was added NaH (60%, 0.2 g, 5 mmol for **10a**; 0.4 g, 10 mmol for **10b**−**d**) at room temperature, and stirring was continued for 40 min under nitrogen. Each 1-acylbenzotriazole (**1a**, 5 mmol; **1c**, 10 mmol; **1g**, 10 mmol; **1c**, 5 mmol, + **1d**, 5 mmol) in THF (30 mL) was added by syringe at room temperature, and the resulting mixture was stirred for 14 h under nitrogen. Water (22 mL), ammonium chloride (0.88 g, 16.5 mmol), and ammonium hydroxide (28.8%, 0.21 mL) were added to the mixture, which was then heated under reflux for 1 h. The same workup was followed as for **6** to give the corresponding products **10**.

General Procedure for the Preparation of *β*-Diketons 13a−c. To a stirred solution of 1-benzoylacetone **10a** (0.81 g, 5 mmol) in THF (30 mL) was added NaH (60%, 0.27 g, 6.6 mmol) at rt, and stirring was continued for 40 min under nitrogen. Each 1-acylbenzotriazole (**1k**,**d**,**g**: 5 mmol) in THF (30 mL) was added by syringe at room temperature, and the resulting mixture was stirred at room temperature for 14 h under nitrogen. Water (22 mL), ammonium chloride (0.88 g, 16.5 mmol), and ammonium hydroxide (28.8%, 0.21 mL) were added to the mixture, which was then heated under reflux for 1 h. The same workup was followed as for **6** to give the corresponding products **13a**−**c**.

General Procedure for the Preparation of O-Acylated Enolates 15a−e. To a stirred solution of ethyl α-monosubstituted acetoacetate **7a** or **7b** (5 mmol) in THF (30 mL) was added NaH (60%, 0.20 g, 5 mmol) at room temperature, and stirring was continued for 40 min under nitrogen. Each 1-acylbenzotriazole (**1m**,**n**,**a**,**c**: 5 mmol) in THF (30 mL) was added to the yellow suspension by syringe at room temperature, and the resulting mixture was stirred for 2−3.5 h. A small amount of silica gel was added to the reaction mixture, and THF was removed under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexanes/chloroform (3/1 → 1/1, v/v) as an eluant to give the corresponding product **15** as a colorless oil.

Acknowledgment. We thank National Institute of Advanced Industrial Science and Technology, Japan, for online Integrated Spectral Data Base System for Organic Compounds.

Supporting Information Available: Characterization data for compounds **6a**−**f**; **8a**,**b**,**h**,**i**,**j**; **8c**−**g**,**k**,**l**; **11**, **10a**−**d**, **12**; **13a**−**c**; and **15a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049274L