Synthesis of β-Dicarbonyl Compounds Using 1-Acylbenzotriazoles as Regioselective C-Acylating Reagents

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1-Acylbenzotriazoles **1** are efficient C-acylation reagents for the regioselective conversion of ketone enolates **2** into β-diketones **3**.

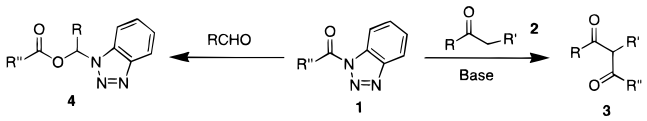
Introduction

Enolate acylations often form mixtures of O- and C-acylation products.[1] The nature of the electrophile, metal counterion, solvent, the reaction temperature, reagent stoichiometry, or structure of the substrate itself have all been shown to influence significantly the regioselectivity of such acylations.[2] Carbon acylations have been widely studied and reviewed.[2,3] The regioselective synthesis of 1,3-diketones and 1,3-ketoesters by the C-acylation of simple ketone enolates has been investigated using a plethora of acylating reagents, including formates and oxalates,[3] anhydrides,[4a] acid chlorides,[4b] dialkyl carbonates,[4c,d] methyl methoxymagnesium carbonate,[4e] *N*-acylimidazoles,[4f] and more recently, acyl cyanides.[4g,h] Indirect methods for carbon acylation utilized for the efficient preparation of β-dicarbonyl compounds include (i) migration of the acyl group from the enol ester,[5a] (ii) umpolung-type carbonyl anion synthons,[5b] (iii) acylation of silyl enol ethers,[5c] and (iv) oxidation of β-hydroxycarbonyl derivatives, obtained by aldol condensations of carbonyl compounds with aldehydes.[5d]

Results and Discussion

1-Acylbenzotriazoles **1** act as efficient O-acylation reagents in their additions to aldehydes to give esters of type **4**.[6] We now demonstrate the C-acylation potential of 1-acylbenzotriazoles **1** in the regioselective preparation of β-diketones **3** from the enolates of ketones **2**. Condensation of the corresponding ketone enolates with acylbenzotriazoles **1**, prepared as previously reported from acid chlorides and benzotriazole[6] (Scheme 1), gave β-diketones **3** as shown in Table 1.

Scheme 1



As is well-known, many β-diketones exist as rapid equilibrium mixtures of keto and enol forms; the equilibrium ratio and the rates of interconversion of the keto and enol form are highly structure-dependent.[7a,b] In the present work, compounds **3a**−**d** were recovered exclusively in the enol form. For all other cases (**3e**−**p**) the keto form predominated in the crude products (Table 1). After purification by chromatography in silica gel, aliphatic diketones **3m**−**o** and highly hindered cyclic ketones such as **3p** were recovered exclusively in the keto forms. In other cases, tautomerism to the enol form was observed during chromatography. More constrained unsaturated cyclic ketones such as **3f,g** showed a higher enol percentage than less constrained **3h**, although all three were recovered as enol/keto mixtures. More steric hindrance in the ring in **3i,l** favored the keto form compared to **3h**. Bulky substituents in the acylating reagent (**3e** and **3i** were recovered mainly in the keto form) also reduced the proportion of enol tautomer (**3j,k** were obtained as enol/keto mixtures). This tautomeric preference is in accord with the results of previously reported theoretical and experimental studies.[7a,b]

Neither O-acylation nor diacylation products were detected when the reaction **1** → **3** was carried out with ketones **2a**−**o**. Among these, unsaturated ketones **2e**−**l** gave only the kinetically favored 1,3-diketones **3e**−**l** and no products resulting from γ-deprotonation were observed. However, the influence of steric effects in the lithium enolates in increasing O-acylation[3] showed up in ketones **2p** (61% of O-acylation isomer was isolated) and **2q** (O-acylation exclusively); in these cases attempts to induce the oxygen-to-carbon acyl-migration by DMAP[8] were unsuccessful. No apparent difference in the yields or O- to C-acylation ratios was observed by quenching the reaction at low temperature or adding HMPA to the reaction mixture. On the other hand, a small excess of the enolate (1.1 equiv) helped to prevent diacylation.

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(5) (a) Kraus, G. A.; Fulton, B. S.; Woo, S. H. *J. Org. Chem.* **1984**, *49*, 3212. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. (c) Le Roux, C.; Mandrou, S.; Dubac, J. *J. Org. Chem.* **1996**, *61*, 3885. (d) Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M. *Synthesis* **1988**, 178.
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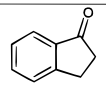
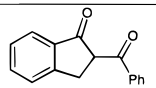
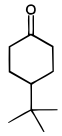
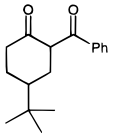
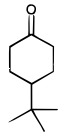
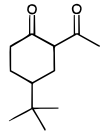
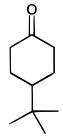
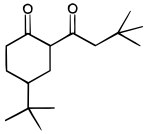
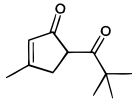
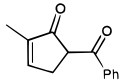
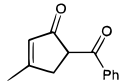
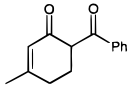
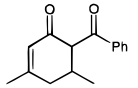
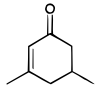
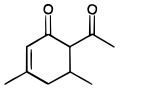
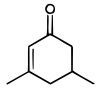
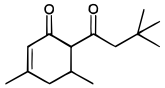
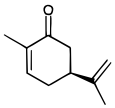
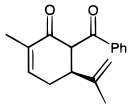
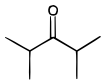
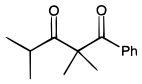
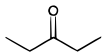
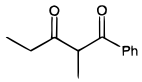
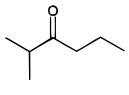
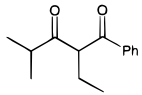
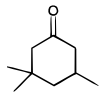
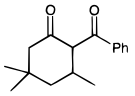
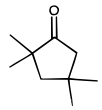
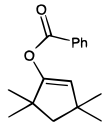
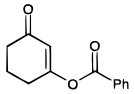
Table 1. Synthesis of β-Dicarbonyl Compounds 3 Using 1-Acylbenzotriazoles 1

Series	Ketone 2	Product 3[a]	Method	Crude Product: Yield 3 (%)[b] (keto+enol)	Crude Product: Keto (%)[c]	After Chromatography: Yield 3 (%)[d] (keto+enol)	After Chromatography: Keto (%)[c]	After Chromatography: Recov. 1 (%)[d]
a			A	86	6	82	6	9
b			A	87	<5	75	<5	10
c			A	>95	<5	93	<5	0
d			A	79	<5	71	<5	18
e			A	92	90	85	87	8
f			A	75	41	63	29	22
g			A	95	59	78	34	0
h			A	92	85	82	48	0
i			A	>95	>95	78	85	0
j			A	94	64	81	28	0
k			A	88	67	75	48	10
l			A	88	59	69	55	0
m			A	>95	-	92	-	0
n			A	86	>95	79	>95	0
o			A	>95	>95	73[e]	>95	0
p			A	48	>95	36[f]	>95	0
q			A	80	-	68	-	17
r			B	55	-	45[g]	-	30

[a] Products were recovered in the keto form, enol form, or mixtures of keto/enol tautomers. [b] Yields determined by ^{1}H NMR of the crude mixtures. [c] Percentages determined by ^{1}H NMR of product **3**. [d] Isolated yields after column chromatography. [e] 7% of the other regioisomer was obtained. [f] 61% of the O-acylated isomer was obtained. [g] 22% of 3-(1*H*-benzotriazol-1-yl)-2-cyclohexen-1-one (**4r**) was obtained.

2-Acylcycloalkane-1,3-diones have been typically prepared in a two-step procedure via O-acylation of the cycloalkane-1,3-diones followed by O−C isomerization of the corresponding enol esters.[9a,b] To investigate the feasibility of this method for enolates generated under thermodynamic control, a one-pot reaction of **1** with 1,3-cyclohexanedione was carried out in the presence of triethylamine as base at 0 °C (method B, **3r**). No C-acylated product was detected in the crude mixture, which was separated by chromatography into the enol ester (45%), the corresponding 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-cyclohexen-1-one (**4r**) (22%), and unreactive 1-benzoylbenzotriazole (30%).

1-Acylbenzotriazoles have been extensively used for the acylation of nitrogen[10a] and oxygen[10b] nucleophiles, but their use for C-acylations has been quite limited. The only literature example located was a C-acylation step in the total synthesis of Spongistatin 2.[11]

We have now demonstrated 1-acylbenzotriazoles to be a new class of regioselective C-acylating reagents for the generation of 1,3-diketones. The protocol for the preparation of β-dicarbonyl compounds appears to be regioselective and quite general for a variety of simple ketone enolates.

Thus 1-acylbenzotriazoles extend and complement the arsenal of reagents for enolate acylations. In general, the more reactive the electrophile, the greater the tendency toward O-acylation.[2] Compared with acid chlorides, the advantage of 1-acylbenzotriazoles rests on their neutral character and easy accessibility. While *N*-acylimidazoles have been successfully used as C-acylating reagents of enolates in total synthesis,[12a,b] they are also less stable than the corresponding 1-acylbenzotriazoles.[13a−c] Acyl cyanides are more reactive than 1-acylbenzotriazoles but less stable[14a] and can undergo nucleophilic attack at the cyanide group.[14b]

The present procedure, combining readily available reagents, simple manipulations and excellent yields, should be valuable for the preparation of 1,3-diketones.

Experimental Section

All reactions were carried out under an atmosphere of argon, unless otherwise specified. Glassware was routinely oven-dried at 160 °C for a minimum of 4 h and then connected to a vacuum line before assembly under a dry argon stream. Anhydrous solvents were obtained by distillation immediately prior to use, from sodium/benzophenone ketyl (tetrahydrofuran) or calcium hydride (dichloromethane). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using deuteriochloroform ($CDCl_3$) as solvent. Column chromatography was carried out on MCB silica gel (230−400 mesh).

General Procedure for the Preparation of *N*-Acylbenzotriazoles (1). To a solution of 1*H*-1,2,3-benzotriazole (11.9 g, 0.1 mol) in anhydrous dichloromethane (CH_2Cl_2) (200 mL), at 0 °C under argon, was added triethylamine (Et_3N) (17 mL, 0.12 mol) via syringe dropwise, followed by addition of the corresponding acid chloride (0.11 mol). The resulting mixture was stirred at room temperature for 30 min. The reaction was quenched at this temperature with hydrochloric acid (2 N, 100 mL), and the organic phase was separated and then washed with hydrochloric acid (2 N, 2 × 50 mL) and water (50 mL) successively. The organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness to give a white powder, which was purified by recrystallization.

1*H*-1,2,3-Benzotriazol-1-yl(phenyl)methanone (1a): colorless needles (98%), mp 112−113 °C [lit.[6] mp 112 °C]; ^{1}H NMR δ 8.38 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 7.9 Hz, 2H), 8.16 (d, J = 8.2 Hz, 1H), 7.70 (t, J = 7.9 Hz, 2H), 7.60−7.50 (m, 3H); ^{13}C NMR δ 166.7, 145.7, 133.6, 132.3, 131.7, 131.4, 130.3, 128.4, 126.3, 120.1, 114.7.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-ethanone (1b): colorless macrocrystals (95%), mp 51−52 °C [lit.[6] mp 51−52 °C]; ^{1}H NMR δ 8.24 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.49 (t, J = 8.1 Hz, 1H), 3.00 (s, 3H); ^{13}C NMR δ 169.4, 146.1, 130.8, 130.2, 126.0, 120.0, 114.2, 23.1.

General Procedure for C-Acylation of Ketone Enolates (Method A). A 100-mL round-bottom flask with septum inlet, fitted with a magnetic stirring bar, rubber septum, and argon inlet, was charged with a solution of LDA (3.3 mmol) 0.15 M in THF (25 mL). The mixture was cooled at −78 °C, and a solution of the ketone **2** (3.3 mmol) in dry THF (15 mL) was added dropwise under argon. After the resulting mixture was stirred for 1 h at this temperature to ensure complete enolate formation, a solution of 1-acylbenzotriazole (3 mmol) in dry THF (10 mL) was added in one pot at −78 °C. The reaction mixture was allowed to warm to room temperature overnight before quenching with water (50 mL). The mixture was diluted with ethyl ether (150 mL), and the organic layer was separated, washed with water (2 × 50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the product was purified by chromatography.

2-Benzoyl-1-indanone (3a): yellow needles (82%), mp 96−97 °C [lit.[15] mp 94−95 °C]; (enol tautomer) ^{1}H NMR δ 15.07 (br s, 1H), 7.95−7.90 (m, 2H), 7.85 (d, J = 8.6 Hz, 1H), 7.60−7.45 (m, 5H), 7.40 (t, J = 7.0 Hz, 1H), 3.87 (s, 2H); ^{13}C NMR δ 195.7, 170.5, 148.5, 137.7, 134.6, 133.2, 131.2, 128.5, 127.9, 127.3, 125.5, 123.3, 109.3, 32.1.

2-Benzoyl-4-(*tert*-butyl)cyclohexanone (3b): brown needles (75%), mp 97−99 °C; (enol tautomer) ^{1}H NMR δ 16.72 (s, 1H), 7.60−7.50 (m, 2H), 7.50−7.30 (m, 3H), 2.70−2.30 (m, 3H), 2.25−2.10 (m, 1H), 2.00−1.80 (m, 1H), 1.50−1.30 (m, 1H), 1.30−1.20 (m, 1H), 0.85 (s, 9H); ^{13}C NMR δ 191.4, 189.5, 137.5, 130.4, 128,1, 127.6, 106.7, 45.2, 33.5, 32.3, 27.6, 27.3, 23.0. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.60. Found: C, 78.94; H, 8.82.

O-Acylation of 1,3-Cyclohexanedione (2r) (Method B). A 100-mL round-bottom flask with septum inlet, fitted with a magnetic stirring bar, rubber septum, and argon inlet, was charged with a solution of 1,3-cyclohexanedione (3 mmol) and 1-benzoylbenzotriazole (3.3 mmol) in THF (30 mL). The mixture was cooled at 0 °C, and triethylamine (Et_3N) (3.3 mmol) was added dropwise under argon. The reaction mixture was allowed to warm to room temperature and stirred overnight before quenching with water (50 mL). The mixture was diluted with ethyl ether (150 mL), and the organic layer was separated, washed with water (2 × 50 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the product purified by chromatography.

3-Oxo-1-cyclohexen-1-yl benzoate (3r): yellow oil (45%);[16] ^{1}H NMR δ 8.15−8.05 (m, 2H), 7.70−7.55 (m, 1H), 7.55−7.40 (m, 2H), 6.07 (s, 1H), 2.68 (t, J = 6.5 Hz, 2H), 2.47 (t, J = 6.5

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Hz, 2H), 2.12 (quintet, J = 6.5 Hz, 2H); ^{13}C NMR δ 199.6, 170.2, 163.0, 133.0, 133.3, 130.0, 128.5, 117.6, 36.6, 28.3, 21.2.

3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-cyclohexen-1-one (4r): white needles (22%), mp 119−120 °C; ^{1}H NMR δ 8.14 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 8.2 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 6.56 (s, 1H), 3.41 (t, J = 6.3 Hz, 2H), 2.62 (t, J = 6.3 Hz, 2H), 2.32 (quintet, J = 6.5 Hz, 2H); ^{13}C NMR δ 198.7, 154.6, 146.9, 131.0, 129.3, 125.3, 120.8, 115.2, 111.9, 36.9, 27.1, 21.3. Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.21; N, 19.71. Found: C, 67.25; H, 5.28; N, 20.07.

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Supporting Information Available: Characterization data for **1c,d** and **3c**−**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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