Novel and Efficient Entry to γ-Aryl-Substituted γ,δ-Unsaturated Ketones, Amides, Nitriles, and Sulfones by Conjugate Additions of 2-Benzotriazolylethylsilanes

Alan R. Katritzky,* Michael V. Voronkov, and Dorin Toader

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

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Introduction

The preparation, biological properties, and synthetic utility of γ,δ-unsaturated compounds are of continuing interest in contemporary chemistry.[1a−c] The method of choice for the preparation of various γ,δ-unsaturated systems is the conjugate addition of alkenylcuprate[1d,c,2a,b] or alkenyllithium reagents[3] to activated double bonds (e.g. α,β-unsaturated ketones). However, this approach is seldom used[4] for the preparation of γ-aryl-substituted derivatives of type **1** which have been made with various degrees of success (i) by coupling arylacetylenes **2**;[5a] (ii) ene−retro-ene rearrangement of **3**;[5b] (iii) by vinylation of zinc homoenolates **4**;[5c] and (iv) C-alkylation of **5**.[5d] Moreover, the methods of Scheme 1 have apparently been limited to γ-aryl-substituted γ,δ-unsaturated carbonyl compounds (esters and ketones).

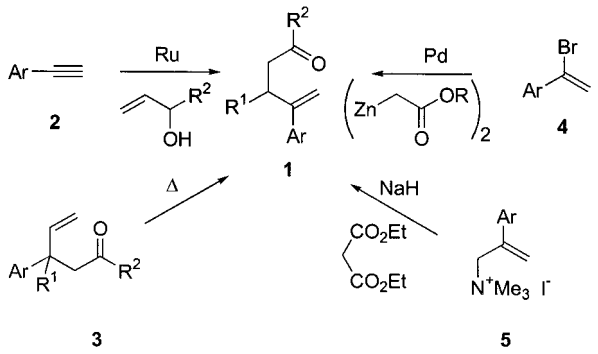
We now report a novel and straightforward route to γ-aryl-substituted γ,δ-unsaturated ketones, amides, nitriles, and sulfones via conjugate addition of 2-benzotriazolyl-2-arylethylsilanes to α,β-unsaturated compounds. This extends our preliminary results[6a] which showed that 2-benzotriazolyl-2-arylethylsilanes reagents can be used as masked α-arylalkenyllithium reagents for the synthesis of γ,δ-unsaturated ketones via conjugate addition to 2-cycloalkenones followed by vicinal elimination of trimethylsilyl and benzotriazolyl groups.

Results and Discussion

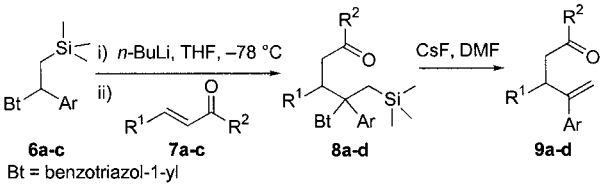
Reagents **6a**−**c** were prepared according to the published procedures in good to excellent yields.[6b] Treatment of **6a**−**c** with 1 equiv of *n*-BuLi at −78 °C in THF, followed by addition of the α,β-unsaturated substrate, afforded the desired products **8a**−**d** (Scheme 2) or **11a**−**d** (Scheme 3).

The results of conjugated additions are summarized in Table 1. The conjugate additions were highly 1,4-regioselective (cf. ref 7) with the exception of mesityl oxide, which gave only a 1,2-adduct. This 1,2-adduct underwent vicinal elimination of the trimethylsilyl and benzotriazolyl groups under the reaction conditions, and 2-[4-(dimethylamino)phenyl]-3,5-dimethyl-3-[(trimethylsilyl)oxy]-1,4-hexadiene (**13**) was isolated as the sole product in 87% yield. An attempt to react **6b** with 4-vinylpyridine gave a complex mixture of products. Attempts to effect such conjugate addition to several α,β-

Scheme 1



Scheme 2

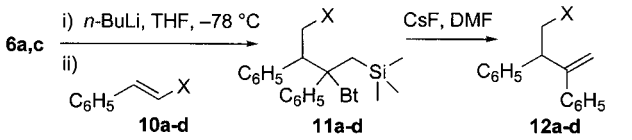


6	Ar
a	4-FC_6H_4
b	4-$Me_2NC_6H_4$
c	C_6H_5

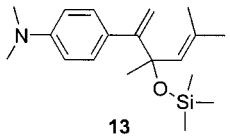
8, 9	Ar	R^1	R^2
a	4-FC_6H_4	-$(CH_2)_3$-	
b	4-FC_6H_4	-$(CH_2)_2$-	
c	4-FC_6H_4	C_6H_5	C_6H_5
d	4-$Me_2NC_6H_4$	C_6H_5	C_6H_5

7	R^1	R^2
a	-$(CH_2)_3$-	
b	-$(CH_2)_2$-	
c	C_6H_5	C_6H_5

Scheme 3



10, 11, 12	X
a	CN
b	$SO_2C_6H_5$
c	NO_2
d	$C(O)N(C_2H_5)_2$



(1) (a) Fry, D. F.; Brown, M.; McDonald, J. C.; Dieter, R. K. *Tetrahedron Lett.* **1996**, *37*, 6227. (b) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983. (c) Naf, F.; Degen, P. *Helv. Chim. Acta* **1971**, *54*, 1939.

(2) (a) De Chirico, G.; Fiandanese, V.; Marchese, G.; Naso, F.; Sciacovelli, O. *J. Chem. Soc., Chem. Commun.* **1981**, 523. (b) Piers, E.; Yeung, B. W. A. *J. Org. Chem.* **1984**, *49*, 4567.

(3) Zweifel, Z.; Hahn, G. *J. Org. Chem.* **1983**, *48*, 1774.

(4) Kende, A. S.; Jungheim, L. N. *Tetrahedron Lett.* **1980**, *21*, 3849.

(5) (a) Derien, S.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1994**, 2551. (b) Srikrishna, A.; Krishnan, K.; Venkateswarlu, S.; Kumar, P. P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2033. (c) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83. (d) Gupton, J. T.; Krolikowski, D.; Rusler, M. *Synth. Commun.* **1989**, *19*, 2415.

(6) (a) Katritzky, A. R.; Toader, D. *J. Am. Chem. Soc.* **1997**, *119*, 9123. (b) Katritzky, A. R.; Voronkov, M. V.; Toader, D. *J. Chem. Soc., Perkin Trans. 2* **1998**, in press.

(7) Katritzky, A. R.; Ming, Q. *Collect. Czech. Chem. Commun.* **1998**, *63*, 699.

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Table 1. Preparation of Compounds 8a−d, 9a−d, 11a−d, and 12a−d

compd	reagent	yield (%)[a] **8** or **11**	yield (%)[a] **9** or **12**	reaction conditions
9a	**6a**	81	50	100 °C, 40 min
9b	**6a**	70	80	100 °C, 40 min
9c	**6a**	*b*	36[c]	100 °C, 1.5 h
9d	**6b**	*b*	47[c]	100 °C, 1 h
12a	**6c**	*b*	66[c]	100 °C, 2.5 h
12b	**6c**	67	78	25 °C, 3 d
12c	**6c**	75		25 °C, 3 d
12d	**6a**	*b*	86	100 °C, 12 h

[a] Yield of isolated product as diastereomeric mixture. [b] Intermediates were subjected to elimination without purification. [c] Yield for two steps.

unsaturated esters led only to extensive polymerization of the substrates.

Adducts **8a−d** and **11a−d** were all isolated as diastereomeric mixtures which were directly subjected to the vicinal elimination of trimethylsilyl and benzotriazolyl groups in the presence of cesium fluoride (the use of TBAF resulted in significant amounts of desilylated products without vicinal elimination of benzotriazole). The elimination proceeded smoothly at 100 °C in DMF affording the desired γ,δ-unsaturated compounds **9a−d** or **12a,b,d** in good yields. Depending on the substrate, reaction time varied from 40 min to several hours with cyclic ketones requiring the shortest time and the amide the longest. Seemingly, the *p*-substituent on γ-aryl (e.g., **9c** vs **9d**) did not significantly alter the rate of elimination. We found that both **11b** and **11d** underwent decomposition under these conditions probably due to facile syn elimination of sulfone or nitro groups. In the case of compound **11b** the elimination was successfully conducted at room temperature to afford **12b** in 78% yield. On the other hand, the corresponding nitro derivative **11c** failed to yield **12c** even under these mild conditions and lead to decomposition. This could be due to the activation of the nitro group by CsF which makes both product and the starting material prone to side reactions.[8]

Conclusion

A number of γ,δ-unsaturated ketones, amides, nitriles, and sulfones are readily prepared from various 2-benzotriazolyl-2-arylethylsilanes. The method described herein is simple and straightforward and allows a variety of substituents.

Experimental Section

General Methods. Melting points were determined with a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230−400 mesh. 1-[1-(4-Fluorophenyl)-2-(trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole (**6a**),[6a] 4-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2-(trimethylsilyl)ethyl]-*N*,*N*-dimethylaniline (**6b**),[6b] and 1-[1-phenyl-2-(trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole (**6c**)[6b] were prepared according to previously reported procedures.

General Procedure for the Preparation of 9a−d and 12a−d. *n*-BuLi in hexanes (1.52 M, 1.38 mL, 2.1 mmol) was added over 5 min to a solution of the appropriate **6** (2 mmol) in THF (50 mL) at −78 °C. After 30 min of stirring, the corresponding compound **7** or **10** was added, and reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was diluted with ethyl acetate (100 mL), and the reaction was quenched with saturated ammonium chloride aqueous solution (50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The remaining oil was dissolved in DMF (4 mL), CsF (0.36 g, 3 mmol) was added to the reaction mixture, and the mixture was heated at 100 °C for the time indicated in Table 1. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (100 mL), and dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting oil was subjected to column chromatography with hexanes:ethyl acetate = 9:1.

3-[1-(4-Fluorophenyl)ethenyl]cyclohexanone (9a): colorless oil; ^1H NMR δ 1.56−1.71 (m, 2H), 1.96−2.05 (m, 2H), 2.25−2.57 (m, 4H), 2.93 (t, J = 10.3 Hz, 1H), 5.05 (s, 1H), 5.19 (s, 1H), 6.98 (t, J = 7.2 Hz, 2H), 7.24−7.28 (m, 2H); ^{13}C NMR δ 24.8, 30.3, 41.2, 42.8, 46.8, 112.2, 115.0 (d, J = 21.8 Hz), 128.2 (d, J = 8.8 Hz), 137.5, 150.9, 161.6 (d, J = 246.8 Hz), 210.9. Anal. Calcd for $C_{14}H_{15}FO$: C, 77.03; H, 6.94. Found: C, 76.98; H, 7.33.

3-[1-(4-Fluorophenyl)ethenyl]cyclopentanone (9b): colorless oil; ^1H NMR δ 1.92 (m, 1H), 2.26−2.71 (m, 5H), 3.48 (br s, 1H), 5.22 (s, 1H), 5.39 (s, 1H), 7.18 (t, J = 8.5 Hz, 2H), 7.47 (m, 2H); ^{13}C NMR δ 28.5, 38.0, 40.9, 44.1, 111.6, 115.0 (d, J = 21.8 Hz), 128.0 (d, J = 8.8 Hz), 137.4, 149.4, 161.4 (d, J = 246.8 Hz), 217.8. Anal. Calcd for $C_{13}H_{13}FO$: C, 76.44; H, 6.43. Found: C, 76.26; H, 6.74.

4-(4-Fluorophenyl)-1,3-diphenyl-4-penten-1-one (9c): glassy oil; ^1H NMR δ 3.57 (dd, 1H, J = 6.6 Hz, J = 17.3 Hz), 3.79 (dd, 1H, J = 6.6 Hz, J = 17.3 Hz), 4.82 (t, 1H, J = 6.6 Hz), 5.27 (s, 1H), 5.48 (s, 1H), 7.09 (t, 2H, J = 8.5 Hz), 7.32−7.78 (m, 10H), 8.04 (d, 2H, J = 8.5 Hz); ^{13}C NMR δ 44.1, 45.5, 113.0, 114.8 (d, J = 21.8 Hz), 126.6, 128.0 (d, J = 8.8 Hz), 128.5, 128.5, 133.1, 137.1, 138.0, 142.1, 150.0, 161.8 (d, J = 246.8 Hz), 198.0; HRMS calcd for $C_{23}H_{20}FO$ (M + 1) 331.1498, found 331.1533.

4-[4-(Dimethylamino)phenyl]-1,3-diphenyl-4-penten-1-one (9d): orange solid; mp 127 °C; ^1H NMR δ 3.12 (s, 6H), 3.64−3.80 (m, 2H), 4.97 (d, 1H, J = 5.8 Hz), 5.18 (s, 1H), 5.58 (s, 1H), 6.64 (d, 2H, J = 8.4 Hz), 7.36−7.73 (m, 10H), 8.12 (d, 2H, J = 8.4 Hz); ^{13}C NMR δ 40.4, 44.3, 44.9, 110.4, 112.1, 126.3, 127.4, 127.9, 128.1, 128.3, 128.4, 129.5, 132.8, 137.2, 142.8, 149.8, 150.3, 198.3; HRMS calcd for $C_{25}H_{26}NO$ (M + 1) 356.2014, found 356.2022

3,4-Diphenyl-4-pentenenitrile (12a): colorless oil; ^1H NMR δ 2.79−2.86 (m, 2H), 4.23 (t, 1H, J = 7.2 Hz), 5.21 (s, 1H), 5.54 (s, 1H), 7.24−7.31 (m, 10H); ^{13}C NMR δ 23.6, 46.6, 114.8, 118.3, 126.7, 127.5, 127.7, 127.8, 128.3, 128.8, 139.5, 144.2, 148.4. Anal. Calcd for $C_{17}H_{15}N$: C, 87.51; H, 6.49; N, 6.00. Found: C, 87.35; H, 6.52; N, 6.15.

3,4-Diphenyl-4-pentene-1-phenyl Sulfone (12b): white solid; mp 112.6 °C; ^1H NMR δ 4.02−4.06 (m, 2H), 4.86 (t, 1H, J = 6.8 Hz), 5.30 (s, 1H), 5.64 (s, 1H), 7.44−7.56 (m, 10H), 7.67−7.72 (m, 2H), 7.82−7.85 (m, 1H), 7.99 (d, 2H, J = 7.7 Hz); ^{13}C NMR δ 45.3, 60.2, 114.9, 126.8, 127.1, 127.7, 127.9, 128.2, 128.2, 128.4, 128.9, 133.2, 139.1, 140.5, 149.2. Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.82; H, 5.80. Found: C, 76.06; H, 5.79.

***N*,*N*-Diethyl-3,4-diphenyl-4-pentenamide (12d):** orange oil; ^1H NMR δ 1.30 (t, 6H, J = 7.0 Hz), 3.04−3.19 (m, 2H), 3.38 (q, 2H, J = 7.0 Hz), 3.47−3.54 (m, 1H), 3.64−3.71 (m, 1H), 4.93 (t, 1H, J = 7.2 Hz), 5.41 (s, 1H), 5.71 (s, 1H), 7.39−7.67 (m, 10H); ^{13}C NMR δ 12.7, 14.2, 38.6, 40.2, 41.7, 46.3, 112.6, 126.3, 126.8, 127.2, 127.9, 128.0, 128.2, 141.9, 142.4, 151.2, 170.2; HRMS calcd for $C_{21}H_{26}NO$ (M + 1) 308.2014, found 308.2014.

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(8) Clark, J. M.; Cork, D. G.; Gibbs, H. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2253.