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Benzotriazolyl-Mediated 1,2-Shifts of Electron-Rich Heterocycles

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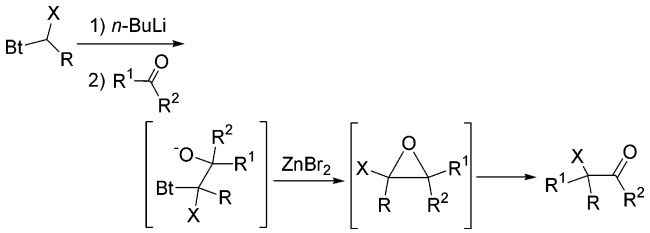
Abstract: The anion formed from the lithiation of 1-[(methylthio)methyl]-1*H*-benzotriazole **1** with *n*-BuLi adds to heteroaryl ketones to give 2-benzotriazolyl alcohols **3a**−**m**. Thermolysis of **3a**−**g** in the presence of zinc bromide induces a 1,2-shift of heteroaromatic groups to form ketones **4a**−**g**. By contrast, in the rearrangement of 2-benzotriazolyl alcohols **3h**,**i**,**k**−**m** migration of the phenyl group rather than the corresponding heteroaromatic groups occurred to give ketones **4h**,**i**,**k**−**m**.

In preceding papers,[1] we described an efficient benzotriazole-mediated insertion of single carbon atoms, carrying aryl, heteroaryl, alkyl, and O-, S-, and N-linked substituents next to a carbonyl group to give α-aryl-, α-heteroaryl, α-alkyl, alkoxyalkyl-, (alkylthio)alkyl-, and (carbazol-9-yl)alkyl-substituted ketones. The mechanism of these rearrangements involves zinc bromide-promoted oxirane ring-closure−ring-opening followed by the migration of that group that can best stabilize an electron deficiency, i.e., H > Ar > *tert*-alkyl > *sec*-alkyl > *n*-alkyl (Scheme 1).

It would be useful if a similar procedure could be applied for the regioselective 1,2-shift of an electron-rich heterocyclic group during the rearrangement in the presence of the competitive alkyl or aryl groups. Such selective shifts are relatively unexplored, although pinacol-type rearrangements provide a few examples of the selective migration of 2-furyl groups,[2] 2-thienyl groups,[2a,3] their benzoanalogues,[3a,c] and 2- and 3-indolyl groups.[3a,c]

To explore the ability of electron-rich heterocycles to migrate in the presence of the alkyl and aryl groups we have now investigated benzotriazole-mediated one-carbon insertions in heteroaryl ketones **2a**−**m** (Scheme 2) and herein report the successful synthesis of homologated ketones **4a**−**i**,**k**−**m** via a 1,2-shift of the diverse heterocyclic groups or a phenyl group as shown in Table 1.

SCHEME 1



SCHEME 2

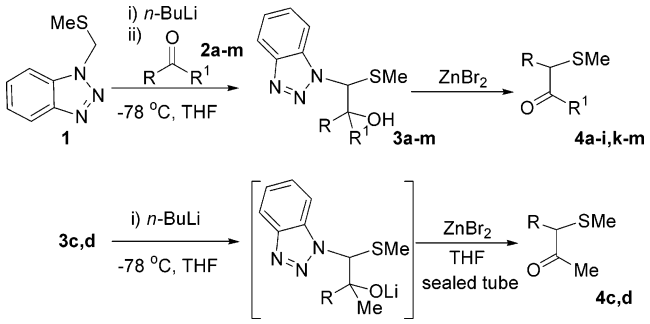


TABLE 1. Preparation of Intermediates 3 and Ketones 4

	2		3	4
	R	R[1]	yield, %[a]	yield, % / solvent / temp. / time
a		Me	82	60 / $ClCH_2CH_2Cl$ / 85°C / 20h
b		Me	85	64 / $ClCH_2CH_2Cl$ / 85°C / 20h
c		Me	82	7 / THF / 100°C / 15h sealed tube
d		Me	72	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
e		Me	75	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
f		Me	94	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
g		Me	40	71 / $Cl_2CHCHCl_2$ / 140°C / 10 min

[a] Yields of mixtures of diastereomers.

Treatment of 1-[(methylthio)methyl]-1*H*-benzotriazole **1** with *n*-BuLi (1 equiv) at −78 °C under a nitrogen atmosphere in THF for 1 h, followed by reaction with the corresponding ketones **2a**−**m** (1 equiv) at −78 °C for 1 h, gave 2-benzotriazolyl alcohols **3a**−**m** in 40−98% yields (Scheme 2, Tables 1 and 2). The intermediates **3a**−**m** were isolated as equal mixtures of two diastereomers and were generally used for the next step without separation. However, in certain cases the pure diastereomeric forms of **3a**−**m** were isolated by recrystallization of the corresponding crude products from acetone−diethyl ether; chromatography also provided enriched samples of each

‡ Dedicated to Professor Makhluf J. Haddadin, my great mentor at the American University of Beirut, Lebanon.

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(2) (a) Gilchrist, T. L.; Stanford, J. E. *J. Chem. Soc., Perkin Trans. 1* **1987**, 225. (b) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 81. (c) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D. *J. Org. Chem.* **1993**, *58*, 5944.

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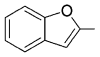
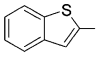
TABLE 2. Preparation of Intermediates 3 and Ketones 4

	2		3	4
	R	R^1	yield, %[a]	yield, % / solvent / temp. / time
h	Ph		75	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
i	Ph		40	23 / $Cl_2CHCHCl_2$ / 85°C / 12h
j	Ph		72	Complex mixture
k	Ph		70	46 / $Cl_2CHCHCl_2$ / 140°C / 1h
l	Ph		98	40 / $Cl_2CHCHCl_2$ / 140°C / 1h
m	Ph		50	58 / $Cl_2CHCHCl_2$ / 140°C / 30 min

[a] Yields of mixtures of diastereomers.

diastereomer. The structures of compounds **3a**−**m** were supported by ^{1}H NMR and ^{13}C NMR spectral data (see the Experimental Section).

All the rearrangements were accomplished in the presence of a 3-fold molar excess of anhydrous zinc bromide. For intermediates **3a**,**b**, the 1,2-shift of the 2- and 3-thienyl groups was effected by refluxing in 1,2-dichloroethane for 20 h to give ketones **4a**,**b** in 61−64% yields (Scheme 2, Table 1).

However, the same reaction conditions applied to the rearrangement of the furyl analogue **3d** were ineffective for the selective transformation to the homologous ketone **4d**. Selective 1,2-migration of the 2-furyl group was enhanced by the reaction of the anion of compound **3d** in THF at 130 °C (sealed tube) to give ketone **4d** in 20% yield (Scheme 2, Table 1).

Heating of compound **3d** in 1,1,2,2-tetrachloroethane at 140 °C for 1 h has been found to be efficient for 1,2-migration of the 2-furyl group to give ketone **4d** in 40% yield (Scheme 1, Table 1). An attempted 1,2-shift of the 1-methylindol-3-yl group in **3c** under various conditions led to complex mixtures from which ketone **4c** was isolated in 7% yield, apparently due to concurrent processes of dehydration or benzotriazole elimination[4] (Scheme 2, Table 1).

Initially, attempts to rearrange the lithium alcoholates of **3e**,**f** failed. The rearrangements of adducts **3e**−**i**,**k**−**m** were achieved optimally in 1,1,2,2-tetrachloroethane at 85 or 140 °C to give ketones **4e**−**i**,**k**−**m** in 23−71% yields (Scheme 2, Tables 1 and 2). Unfortunately, an attempted 1,2-shift of the 1-methylindol-3-yl group in **3j** under various conditions led to complex mixtures.

Significantly, the heteroaromatic group of adducts **3a**−**g** adjacent to the hydroxylated carbon was found in all cases to shift more rapidly than the methyl group. This resulted in the formation of ketones **4a**−**g**. The ^{1}H NMR analysis of **4a**−**g** shows that the protons of the methyl group and the proton of the methine group both resonate as singlets with no spin−spin coupling between them. This observation precludes migration of the methyl group. For the intermediates **3h**,**i**,**k**−**m**, the migration of phenyl group occurred rather than the corresponding heteroaromatic groups to give ketones **4h**,**i**,**k**−**m**.

In the ^{1}H NMR spectra of ketones **4h**,**i**,**k**−**m**, the methine proton signals appear at 4.55−4.80 ppm, which is about 1 ppm at higher field than the signals of the methine proton in the ^{1}H NMR spectra of **4a**−**g** (5.57−5.80 ppm). Moreover, for ketone **4k** the irradiation of the methine proton at 5.59 ppm resulted in a clear NOE effect on the *o*-phenyl protons at 7.97−7.95 ppm. The structures of compounds **4e**−**i**,**k**−**m** were supported by their ^{1}H NMR and ^{13}C NMR spectra.

In conclusion, to extend the synthetic utility of benzotriazolyl-mediated one carbon insertion, the migratory aptitude of π-electron-rich heterocycles of 2-benzotriazolyl alcohols **3a**−**m** in the presence of alkyl and aryl groups has been investigated. Rearrangements of the adducts **3a**−**g** accompanied by a 1,2-shift of heteroaromatic groups gave the one-carbon homologated ketones **4a**−**g** and should find utility in the synthesis of ketones bearing asymmetric centers adjacent to heterocycles. In contrast, in the rearrangement of 2-benzotriazolyl alcohols **3h**,**i**,**k**−**m** the phenyl group migrated preferably to give the one-carbon homologated ketones **4h**,**i**,**k**−**m**.

Experimental Section

1-[(Methylthio)methyl]-1*H*-benzotriazole **1** was prepared according to a previously reported procedure.[5]

General Procedure for the Preparation of Intermediates 3a−m. A solution of **1** (5.58 mmol) in THF (50 mL) under nitrogen was cooled to −78 °C, and a solution of *n*-BuLi (5.58 mmol, 1.58 M in hexane, 3.57 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h, and a solution of the appropriate ketone (5.58 mmol) in THF (15 mL) was added. Each mixture was stirred for an additional 1 h at −78 °C. An aqueous solution of ammonium chloride was then added (30 mL), and each reaction mixture was extracted with diethyl ether. The extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residues were purified by column chromatography on silica gel to give **3a**−**m** as equal mixtures of two diastereoisomers. In certain cases, the isolation of the diastereomeric pure forms was effected by a single recrystallization from a mixture of acetone and diethyl ether (1:1).

General Procedure for the Preparation of Intermediates 4a,b. To a solution of **3a** or **3b** (mixtures of two diastereoisomers) (0.3 g, 0.98 mmol) in 1,1,2,2-tetrachloroethane (15 mL) under nitrogen was added a solution of zinc bromide (2.95 mmol, 1 M in tetrahydrofuran, 2.95 mL, and the reaction mixture was heated at 140 °C for 20 h. The reaction mixture was concentrated under reduced pressure and residue purified by column chromatography on silica gel to give **4a**,**b**.

General Procedure for the Preparation of Ketones 4e−i,k−m. To a solution of **3e**−**i**,**k**−**m** (mixtures of two diastereoisomers) (0.57 mmol) in 1,1,2,2-tetrachloroethane (15 mL) under nitrogen was added a solution of zinc bromide (1.71 mmol, 1 M in tetrahydrofuran), and the reaction mixture was heated at 140 °C for periods from 10 min to 1 h (see Tables 1 and 2). Each reaction mixture was concentrated under reduced pressure and the corresponding residue purified by column chromatography on silica gel to give **4e**−**i**,**k**−**m**.

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(±)-1-(1-Methyl-1*H*-indol-3-yl)-1-methylthiopropan-2-one (4c). A solution of **3c** (mixture of two diastereomers) (0.4 g, 1.14 mmol) in THF (15 mL) was cooled to −78 °C, and a solution of *n*-BuLi (1.14 mmol, 1.58 M in hexane, 0.73 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h under nitrogen, and a solution of zinc bromide (3.40 mmol, 1 M in tetrahydrofuran, 3.40 mL) was added. The reaction mixture was heated in a sealed tube at 100 °C for 15 h, and after cooling, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **4c** as a brown oil (7%). ^{1}H NMR ($CDCl_3$): δ 7.64−7.61 (m, 1H), 7.34−7.23 (m, 3H), 7.17−7.12 (m, 1H), 4.82 (s, 1H), 3.79 (s, 3H), 2.27 (s, 3H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 203.1, 146.2, 137.0, 128.4, 126.8, 122.2, 119.6, 119.0, 109.5, 52.0, 32.9, 13.9. Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.99; H, 6.51; N, 6.03.

(±)-1-(2-Furyl)-1-(methylthio)acetone (4d). Method A. A solution of **3d** (mixture of two diastereomers) (0.4 g, 1.38 mmol) in THF (15 mL) under nitrogen was cooled to −78 °C, and a solution of *n*-BuLi (1.38 mmol, 1.58 M in hexane, 0.9 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 1 h, and a solution of zinc bromide (6.50 mmol, 1 M in tetrahydrofuran, 6.5 mL) was added. The reaction mixture was heated in sealed tube at 130 °C for 80 h and after cooling was poured into 1 N aqueous hydrochloric acid (10 mL). The reaction mixture was extracted with diethyl ether. The ether solution was washed with water, dried over potassium carbonate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **4d** as a colorless oil (21%). ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J = 1.1 Hz, 1H), 6.45 (d, J = 3.1 Hz, 1H), 6.38−6.36 (m, 1H), 4.55 (s, 1H), 2.29 (s, 3H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 200.1, 148.0, 142.7, 110.6, 109.5, 52.6, 26.8, 13.7. Anal. Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92; Found: C, 56.65; H, 5.98. The spectral data of this compound is identical to that reported in the literature.[6]

Method B. To a solution of **3d** (mixture of two diastereomers) (0.69 mmol) in 1,1,2,2-tetrachloroethane (15 mL) under nitrogen was added a solution of zinc bromide (2.1 mmol, 1 M in tetrahydrofuran), and the reaction mixture was heated at 140 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography on silica gel to give **3d** (40%).

Supporting Information Available: Characterization data for compounds **3a**−**m** and **4a**,**b**,**e**−**i**,**k**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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