ORGANIC LETTERS

2000
Vol. 2, No. 24
3789−3791

$BtCH_2TMS$-Assisted Homologation of Carboxylic Acids: A Safe Alternative to the Arndt–Eistert Reaction

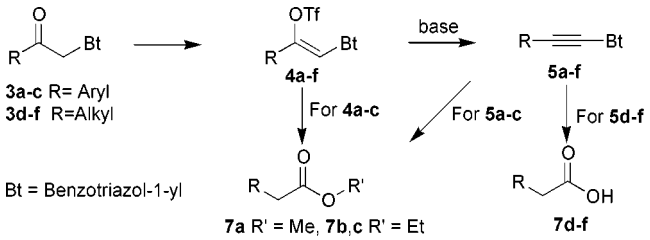
Alan R. Katritzky,* Suoming Zhang, and Yunfeng Fang

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

katritzky@chem.ufl.edu

Received August 23, 2000

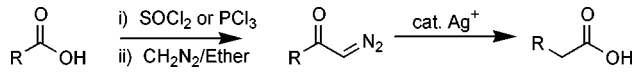
ABSTRACT



One-carbon homologation of carboxylic acids is achieved by (i) treatment of an acyl chloride with 1-[(trimethylsilyl)methyl]-1*H*-1,2,3-benzotriazole ($BtCH_2TMS$) (1) to afford *N*-(acylmethyl)benzotriazoles 3a–f, followed by (ii) conversion of 3a–f with triflic anhydride into $RC(OTf)=CHBt$ 4a–f, and (iii) the subsequent reaction of 4a–c with $NaOCH_3$ followed by 1N HCl to afford esters RCH_2CO_2R' 7a-c in overall yields of 50–70%. For the aliphatic compounds 5d–f, treatment of 5d–f with *p*-toluenesulfonic acid followed by TBAF/THF afforded acids RCH_2COOH 7d–f.

The Arndt−Eistert reaction is the most important and most commonly used procedure for converting a carboxylic acid into its higher homologue acid or acid derivative, such as an ester or amide. An intermediate α-diazomethyl ketone undergoes the Wolff rearrangement in the presence of silver oxide or silver benzoate as a catalyst (Scheme 1).

Scheme 1. The Arndt−Eistert Reaction



The Arndt−Eistert reaction is widely used in organic synthesis.[1] However, this classical procedure suffers from certain handling difficulties and limitations for large scale preparation. α-Diazomethyl ketones are hazardous and are strong skin irritants.[2] Moreover, to achieve high overall yields, the intermediate diazo compounds often have to be recrystallized and freshly prepared silver benzoate is required. Modified Arndt−Eistert procedures ease these difficulties only in part.[3] Alternative one-carbon homologations of carboxylic acids include (i) Kowalsky's CH_2Br_2 method,[4] which requires the use of a strong base and gives 53−80% yields and (ii) Barton's radical homologation,[5] where light-sensitive *O*-acyl-*N*-hydroxyl-2-thiopyridones are the key intermediates.

In this letter, we report a convenient and safe alternative for acid homologation with the one-carbon synthon $BtCH_2$-TMS (**1**), utilizing the anion stabilizing and leaving group properties of benzotriazole.[6] $BtCH_2TMS$ (**1**) and *N*-(acyl-

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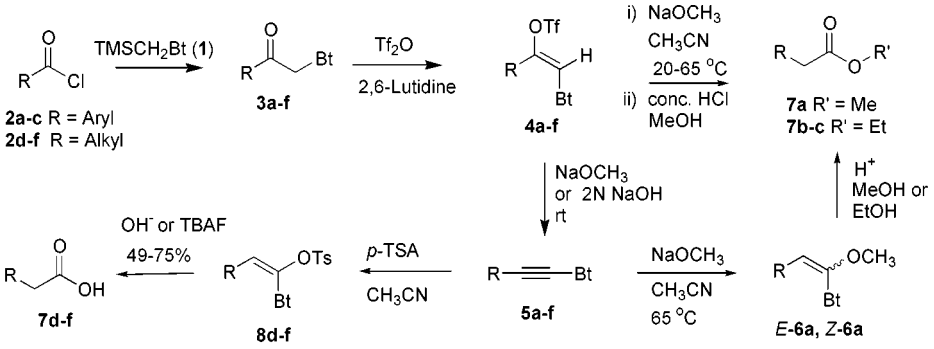
10.1021/ol0002370 CCC: $19.00
Published on Web 10/31/2000

Scheme 2



methyl)benzotriazoles **3a**−**f** were prepared according to the literature procedures in good yields.[7] *N*-(Acylmethyl)benzotriazoles **3a**−**f** were each treated with triflic anhydride (Tf_2O) in the presence of 2,6-lutidine at 0−20 °C to afford stereospecifically *E*-enol triflates **4a**−**f** in excellent isolated yields (>90%, see Table 1 and Scheme 2). No *trans*-isomers were detected in the NMR spectra of the crude products: for instance, irradiation of the vinylic proton of **4a** at 7.59 ppm showed no NOE between the phenyl group and the vinylic proton, indicating that they are mutually *trans*.

Table 1. One-carbon Homologation of Carboxylic Acids 2 to Esters 7

		isolated yields, %			
	R	**3**	**4**	**5**	**7**
2a	C_6H_5	85[7]	95	98[9]	89[a]
2b	*p*-ClC_6H_4	90	95	97	98[a]
2c	*p*-$CH_3C_6H_4$	91[7]	90	95[9]	92[a]
2d	CH_3	83[7]	88	90	55[b]
2e	$(CH_3)_3CCH_2$	95	95	91	45[b]
2f	*n*-$CH_3(CH_2)_6$	95	90	92	49[b]

[a] Isolated yield from **4**. [b] Yield from **5**.

Enol triflates **4a**−**f** reacted with 2.5 equiv of $NaOCH_3$ in acetonitrile at 20 °C to give alkynyl-1*H*-1,2,3-benzotriazoles **5a**−**f** which could be isolated in quantitative yields. The effects of the base and solvent are small: use of 2 N NaOH/THF or $NaOCH_3/CH_3CN$ gave similar results. For aromatic compounds **4a**−**c**, further reflux of the reaction mixture at 65 °C followed by hydrolysis with concentrated HCl in an alcohol afforded directly the corresponding homologated esters **7a**−**c**. The reaction sequence is shown in Scheme 2. Treatment of **5a** with 1.2 equiv of $NaOCH_3$ in acetonitrile at 65 °C for 2 h regioselectively generated 1-[(*E*)-1-methoxy-2-phenylethenyl]-1*H*-1,2,3-benzotriazole *E*-**6a** (R = Ph)[8] as the major product and 1-[(*Z*)-1-methoxy-2-phenylethenyl]-1*H*-1,2,3-benzotriazole *Z*-**6a** (R = Ph)[8] as the minor product. No regioisomers were detected. NOE experiments of *E*-**6a** displayed positive NOE between OCH_3 group and vinylic proton when the vinylic proton at 6.11 ppm was irradiated. The ratio of *E*/*Z*-**6a** is from 74:26 to 80:20.

The mixtures of *E*-**6a**,**b** and *Z*-**6a**,**b** were hydrolyzed with concentrated HCl in methanol or ethanol yielding the homologated methyl ester **7a** or ethyl ester **7b** in good yields, respectively. In fact, the enol triflates **4a**−**c** readily converted into the desired esters **7a**−**c** after treatment in situ with $NaOCH_3$ in acetonitrile followed by concentrated HCl in an alcohol successively in excellent yields without the isolation of the intermediates **5a**−**c** and **6a**−**c** (Table 1).

The procedure was modified for the aliphatic derivatives **4d**−**f**: these compounds were treated with 2.2 equiv of $NaOCH_3$ in CH_3CN (or with 2N NaOH in THF) at 20 °C for 1 h. After workup, 1-alkynylbenzotriazoles (**5d**−**f**) were obtained in quantitative yield (Table 1, entries 4−6). This is the first synthesis of an 1-alkynylbenzotriazole, compounds that cannot be obtained by direct alkynylation of benzotriazole.[9] However, after further reflux of the reaction mixture, none of the desired addition product analogous to **6a**−**c** was detected. Fortunately, treatment of **5d**−**f** with *p*-toluenesulfonic acid monohydrate in acetonitrile at 65 °C for 4−6 h generated enol toluenesulfonates **8d**−**f** in 62−75% yield together with about 5−10% of the starting **3d**−**f** and 5−10% of the hydrolyzed product **7d**−**f**. Hydrolysis of isolated **8d**−**f** with 1 equiv of TBAF in THF at 70 °C provided the corresponding acids **7d**−**f** (65−80%). This two-step procedure could be carried out in one-pot by direct treatment of **5d**−**f** with *p*-toluenesulfonic acid followed by the hydrolysis of **8d**−**f** with TBAF in THF without the isolation of the intermediate **8d**−**f**, but gave a lower yields of **7d**−**f** (40−55%).

In summary, a concise and practical procedure for the transformation of acids into one-carbon homologated acid derivatives has been developed using readily available, versatile, and high-yielding reagent $BtCH_2TMS$ (**1**), and this procedure is apparently applicable for both aromatic and aliphatic carboxylic acid derivatives. This novel approach

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extends the scope of utilization of benzotriazole compounds and of homologation chemistry.

Supporting Information Available: Experimental procedures and characterization for compounds **3b**,**e**,**f**, **4a**−**f**, **5a**−**f**, *E*,*Z*-**6a** and **8d**−**f**, ^{1}H NMR, and ^{13}C NMR spectra for **3e**, **4a**−**f**, **5b**,**d**−**f**, *E*,*Z*-**6a**, and **8d**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0002370