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21. 10 mL of 1 N HCl was added to **4** and refluxed for 15 h in order to hydrolyze the most weak C-N(N^+Me_2)(C=O) bond of **4**. The hydrolyzed polymer was collected with 20 mL of methylene dichloride for 3 times.

The New Procedure for the Preparation of α-Trifluoromethylated Arylacetamides

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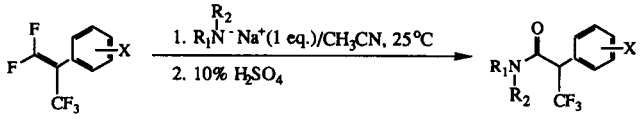
Trifluoromethylated organic molecules have recently been received much attention because of their unique properties in the areas of materials, pharmaceuticals and agrochemicals.[1,2] α-Trifluoromethylated arylacetamides, in particular, are very important synthetic intermediates for the preparation of biologically active compounds. For examples, hydrolysis of α-trifluoromethylated arylacetamides provides α-trifluoromethylated arylacetic acids which are potential antiinflammatory agents such as trifluoro-analog of ibuprofen and naproxen.[3] 3,3-Difluoro-2-arylallylamines,[4] potential monoamine oxidase inhibitors, can also be prepared from the reduction followed by HF-elimination reaction of α-trifluoromethylated arylacetamides.

Although numerous methods for the synthesis of trifluoromethylated compounds have been developed in last two decades,[5,6] there are only limited reports on the synthesis of α-trifluoromethylated arylacetamides. These reports involve the reaction of the electrochemically generated trifluoromethyl radical with acrylamide[7] and chlorination of α-trifluoromethylated acids, followed by reaction of amines.[8] In recent years, it has been also reported that hydrogenation of α-hydroxy-α-(trifluoromethyl)arylacetamide which can be prepared *via* α,α,α-trifluoroacetophenone cyanohydrin provided α-trifluoromethylated arylacetamides.[9] However, these methods have disadvantages such as low yields, multistep procedure and lack of generality. As an alternative approach to overcome these synthetic drawbacks, we decided to use β,β-difluoro-α-trifluoromethylstyrenes **1**[10] as a trifluoromethylated building block. In this communication, we wish to describe about the addition-elimination of β,β-difluoro-α-trifluoromethylstyrene derivatives with sodium alkylamides, followed by hydrolysis as one pot procedure for the preparation of α-trifluoromethylated arylacetamides.

When β,β-difluoro-α-trifluoromethylstyrene **1a** was reacted with 1 equiv. of sodium *n*-butylamide in acetonitrile at room temperature, only monosubstituted product **2a** was obtained in 67% yield. We anticipated that deprotonation of **2a** by excess sodium *n*-butylamide afforded imine anion (or metalloenamine) which undergoes β-defluorination to give ketenimine. The formed ketenimine is further reacted with sodium *n*-butylamide, followed by hydrolysis, to yield α-trifluoromethylated arylacetamide **3a**. However, the treatment of **1a** with 3 equiv. of sodium *n*-butylamide in acetonitrile under the same reaction condition did not provide **3a**, while a messy reaction mixture was formed. An alternative approach to give α-trifluoromethylated arylacetamide **3a** is the hydrolysis of monosubstituted product **2a**. Therefore, the reaction of **1a** with 1 equiv. of sodium *n*-butylamide in acetonitrile followed by treatment of 10% H_2SO_4 afforded **3a** in 85% yield. The use of HCl or $MgSO_4$ instead of H_2SO_4 provided the similar result, but the basic condition needed a prolonged reaction time. The reactions of **1a** with isopropylamine, *t*-butylamine and benzyl amine anions, followed by hydrolysis also provided **3b**, **3c** and **3d** in 86%,

Table 1. Reactions of α-trifluoromethyl-β,β-difluorostyrene **1** with sodium alkylamides



1 **3**

Product No.	X	R_1	R_2	Yield (%)[a]
3a	H	*n*-C_4H_9	H	85
3b	H	*i*-C_3H_7	H	86
3c	H	*t*-C_4H_9	H	70
3d	H	$C_6H_5CH_2$	H	67
3e	H	C_2H_5	C_2H_5	61
3f	H	H	H	82
3g	3-CH_3	*n*-C_4H_9	H	79
3h	4-CH_3	*n*-C_4H_9	H	83
3i	4-F	*n*-C_4H_9	H	88
3j	4-Cl	*n*-C_4H_9	H	72
3k	4-CH_3O	*n*-C_4H_9	H	80
3l	4-Cl	*n*-C_4H_9	H	72

[a] Isolated yields.

70% and 67% yields, respectively. The treatment of **1a** with 1 equiv. sodium diethylamide under the same reaction condition resulted in the formation of **3e** in 61% yield. When **1a** was reacted with aniline anion followed by hydrolysis of 10% H_2SO_4, however, a messy reaction mixture was observed and the desired product was not detected. The results for the reactions of **1** with different types of sodium alkylamides are shown in Table 1.

A plausible mechanism for the formation of **3a** can be proposed as shown in Figure 1. Initial attack of sodium *n*-butylamide on **1a** resulted in the formation of **2a** *via* addition and β-defluorination. Protonation of **2a** followed by hydration provided intermediate [I] which underwent dehydrofluorination to give **3a**.

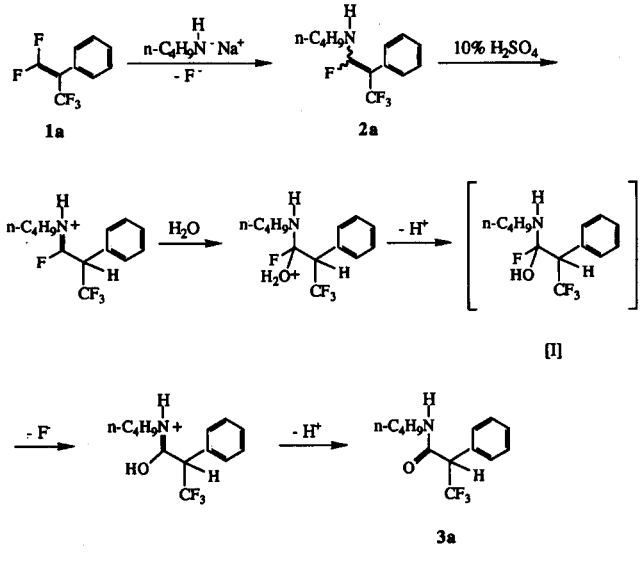
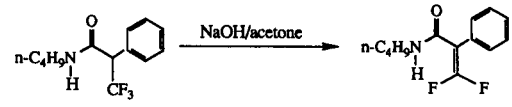


Figure 1. A plausible mechanism for the formation of α-trifluoromethylated arylamide **3a**.

As an approach to prepare β,β-difluoroacrylamides, dehydrofluorination of **3a** with base was performed. Therefore, the treatment of **3a** with NaOH in acetone resulted in the formation of **4a** in 70% yield. In this reaction, the solvent system is quite important. The use of acetonitrile or THF as a solvent did not proceed this reaction and thus the starting material was always recovered. Generally, dehydrofluorinaton reactions of α-trifluoromethylated ketones, esters, and amides with base are face with a difficulty to complete the reaction.[11] A detailed study for the formation of **4a** and synthetic utility of this reaction are now in progress.



3a **4a**

A typical reaction procedure is as follows. To a dry acetonitrile (8 mL) solution of *n*-butylamine (0.146 g, 2.0 mmol) was added sodium hydride (0.08 g, 60% dispersed in oil, 2.0 mmol) at room temperature, and the reaction mixture was stirred for 30 min. under argon atmosphere. 1-Trifluoromethyl-2,2-difluorostyrene (0.416 g, 2.0 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at 0 °C for 20 min. followed by warming to room temperature. Then, 10% sulfuric acid (8 mL) was added to the reaction mixture and stirred for another 30 min. The reaction mixture was poured on water and extracted with ethyl ether. The ethyl ether solution was dried and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (4 : 1) provided N-butyl-2-phenyl-3,3,3-trifluoropropanamide (**3a**) (0.440 g, 85%). **3a**: white solid, mp 52 °C; ^{1}H NMR ($CDCl_3$, TMS) δ 7.50-7.32 (m, 5H), 6.12 (br, s, 1H), 4.23 (q, *J*=8.0 Hz, 1H), 3.30-3.20 (m, 2H), 1.54-1.36 (m, 2H), 1.35-1.18 (m, 2H), 0.88 (t, *J*=7.0 Hz, 3H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −66.55 (d, *J*=8.0 Hz, 3F); MS, m/z (relative intensity) 259 (M^+, 22), 160 (31), 159 (14), 140 (47), 109 (23), 100 (66), 57 (100), 41 (13); IR (KBr) 3200, 2850, 1630, 1520, 1440, 1220, 1120, 1080, 860, 820, 700, 680, 560 cm^{-1}.

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Orthocyclophanes. 7.[1] [1_4]Ketonand: Unexpected Formation and Its Rationalization by Calculation

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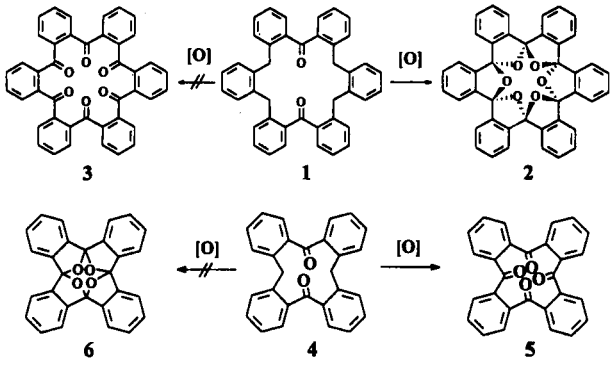
The chemistry of [1_n]orthocyclophane ([1_n]OCP) is of current interest in connection with the preparation of new macrocyclic compounds.[1-6] Systematic studies of [1_n]OCPs have shown that there are remarkable differences between the properties of even- and odd-numbered [1_n]OCPs-whereas oxidation of the benzylic methylenes in even-numbered [1_n]OCPdiones (n=6 or 8, **1** for n=6) provided the star-shaped cyclic polyketals ([1_n]starands, n=6 or 8, **2** for n=6)[4] instead of the polyoxo [1_n]orthocyclophanes ([1_n]ketonands, **3** for n=6), oxidation of all remaining methylenes in odd-numbered [1_n]OCPdiones (n=5, 7, and 9) resulted in the formation of [1_n]ketonands (n=5, 7, and 9).[5] This result suggested the generation of [1_4]starand from oxidation of [1_4]OCPdione (**4**). Herein, the unexpected formation of [1_4]ketonand (**5**) by oxidation of methylenes in [1_4]OCPdione (**4**) with ceric ammonium nitrate (CAN) is described and rationalized by semi-empirical quantum-mechanical MNDO calculations.

In contrast to oxidation of [1_n]OCPdiones (n=6 or 8), further oxidation of the dione **4**[6] with CAN in hot CH_3CN for 6 days gave not the expected [1_4]starand (**6**), but [1_4]ketonand (**5**) in 61% yield.[7] The formation of [1_4]ketonand was confirmed by spectroscopic evidence (vide infra).

The ^{13}C NMR resonance at δ 194.06 and the IR absorption at 1660 cm^{-1} revealed the presence of the carbonyl group. The exact mass (M^+ 416.1049) agreed with the calculated value for $C_{28}H_{16}O_4$ (M 416.1046).



The energy calculation had been attempted by Cho *et al.* who had performed an *ab initio* study on model compounds in which the phenyl rings of **5** and **6** were replaced by simpler C=C bonds.[8] In the present work, we carried out a semi-empirical quantum-mechanical MNDO calculation implemented in the GAMESS package[9,10] on the full compounds without any simplification. The geometry was fully optimized in a C_1 symmetry (that is, without any symmetry restriction) by using the quasi-Newton-Raphson procedure[11] until a root-mean-square gradient less than 3.3×10^{-6} hartree/bohr (=0.0036 kcal/mol/Å) was reached. At each optimized geometry, all the vibrational frequencies were calculated to be real, indicating that the obtained structure corresponds to the true minimum. The optimized structure of **6** is in almost perfect agreement with that obtained by Cho *et al.*[8] In the case of **5**, however, the direction of the carbonyl bonds was calculated to be somewhat different from those of Cho *et al.* This suggests the necessity of the explicit treatment of phenyl rings in the investigation of [1_n]OCPs, since the arrangement of oxygen atoms determines the cavity size, which is a very important property in their application as an ionophore.

The comparison of the energies of the two optimized structures shows that **5** is more stable than **6** by 76.8 kcal/mol. This is in good agreement with the *ab initio* results of Cho *et al.*,[8] and supports the present experimental observation that **5** was formed instead of the expected **6**. The optimized structures are shown in Figures 1 and 2 in order to elucidate why **6** is less stable than **5**. The distances between the oxygen atoms were calculated to be around 2.3 Å for **6**, which are much shorter than the sum of van der Waals radii of two oxygen atoms, 3.0 Å (see the CPK representation in Figure 1b).[12] For **5**, the oxygen-oxygen distances were calculated to be 3.2-4.6 Å. Moreover, the calculation shows that each oxygen atom of **6** carries a slightly more negative charge of −0.34e than −0.27e of **5**. Thus, there is a larger electrostatic and steric repulsion between the oxygen atoms in **6** than **5**, and this explains in part why

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