JOC Article

Ionic Liquid, Surrogate Hydrogen Bromide Reagent for Ring Opening of Cyclopropyl Ketones

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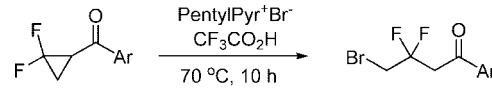
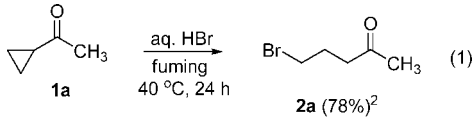


Ionic liquid reagents created by addition of 1 equiv of either CF_3CO_2H or CF_3SO_3H to *N*-pentylpyridinium bromide exhibit excellent chemical reactivities as surrogate HBr reagents in ring-opening reactions of cyclopropyl ketones as well as of 2,2-difluorocyclopropyl ketones to form the respective 3-bromopropyl or 3-bromo-2,2-difluoropropyl ketones in good to excellent yields.

Introduction

The ring opening reaction of hydrogen halides with cyclopropyl ketones to form γ-halo ketones has been known for more than 100 years.[1] The scope and mechanism of the reaction was examined in 1985,[2] but only rarely has this reaction been used as a synthetic method (eq 1).[3] Bromides such as **2a** have been synthesized mostly from other precursors,[4] but when converting cyclopropyl ketones, other reagents have generally been used.[5–7]



We wish to report the use of a mild, ionic liquid-based hydrobrominating agent that has proved extremely effective in carrying out the ring-opening hydrobromination of cyclopropyl ketones. Although ionic liquids have become recognized to be very useful *solvents* for a large variety of reactions, under appropriate conditions and in combination with other compounds they can also be converted into unique reagents.[8] In the present case, when *N*-pentylpyridinium bromide is melted at 70 °C and mixed with 1 equiv of trifluoroacetic acid, it forms an ionic liquid hydrobrominating reagent that remains liquid at room temperature, which lacks any characteristic of volatile HBr, but yet acts very much as a potent surrogate HBr reagent. In related work, other ionic liquid halides, when combined with Bronsted acids, have been used to convert alcohols to alkyl halides,[9–11] and in earlier work our specific reagent was used to carry out stereoselective addition of HBr to alkynoic acids and esters.[12]

In this paper, we report, first, the general use of this reagent to carry out the ring opening of cyclopropyl ketones to form γ-bromo ketones in good to excellent yields and, second, its use to prepare 3-bromo-2,2-difluoropropyl aryl ketones, a new class of fluorinated building blocks that was previously unreported.[13]

Results

All of the required 2,2-difluorocyclopropyl aryl ketones **3a**−**d** were prepared by the synthetic sequence depicted in Scheme 1. The 3-chloropropanones were prepared as described by Sauvage et al.,[14] with the α,β-unsaturated ketones being prepared as described by Krische et al.[15] Finally, the addition

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SCHEME 1. Synthesis of Difluorocyclopropyl Ketones 3a−d

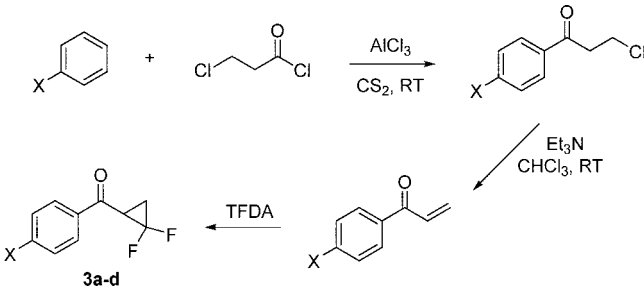
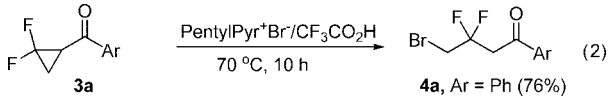


TABLE 1. Reaction of *N*-PentylPyr$^+$Br$^-$/CF_3CO_2H with Fluorinated Cyclopropyl Ketones

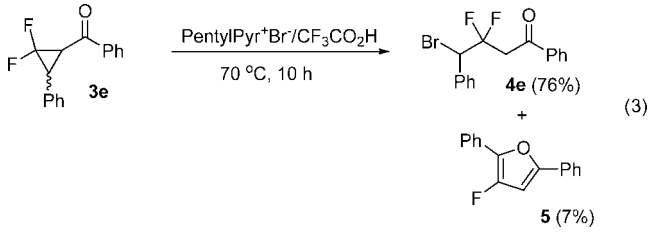
compd	Ar	product (%)
3a	Ph	**4a** (76)
3b	4-ClC_6H_4	**4b** (78)
3c	4-$CH_3C_6H_4$	**4c** (71)
3d	4-$CH_3OC_6H_4$	**4d** (74)

of difluorocarbene to form the difluorocyclopropyl ketones was accomplished using trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA) as the source of CF_2:,[16] and the yields and characterization data for the difluorocyclopropyl ketones are provided in the Experimental Section. Ketone **3e** was prepared according to the procedure of Xu and Chen.[17]

As indicated above, when 1 equiv of trifluoroacetic acid is added to molten *N*-pentylpyridinium bromide, an ionic liquid reagent is formed that behaves effectively as an acidic, hydrobrominating agent, working most selectively in its reactions with 2,2-*difluoro*cyclopropyl aryl ketones, as seen in eq 2 and from the results in Table 1.



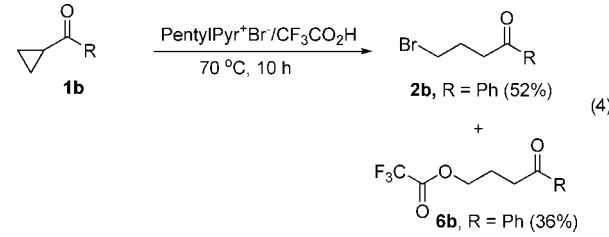
When the reaction is carried out on phenyl-substituted cyclopropyl ketone **3e**, a small amount (7%) of furan product **5** is observed in addition to expected product **4e** (eq 3). This furan is likely formed via cyclization of the intermediate enolic benzylic cation.



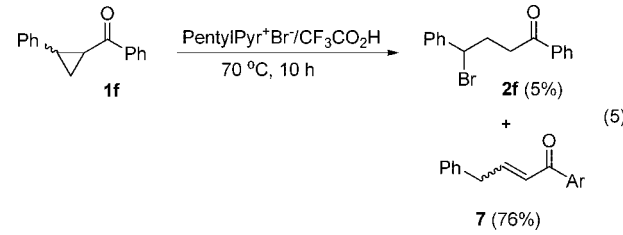
When nonfluorinated ketones are used in this reaction, trifluoroacetate competes with bromide as the nucleophile in the ring-opening process, so that trifluoroacetate products (**6**) are formed as significant minor products in each case (eq 4) and Table 2. Note that the aliphatic ketone system **1a** gives results that are much the same as observed for the aromatic ketone systems.

TABLE 2. Reaction of *N*-PentylPyr$^+$Br$^-$/CF_3CO_2H with Nonfluorinated Cyclopropyl Ketones

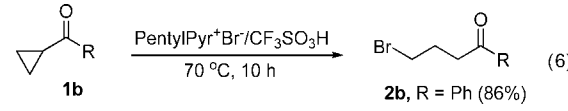
compd	R	product (%)
1a	CH_3	**2a** (64) + **6a** (27)
1b	Ph	**2b** (52) + **6b** (36)
1c	4-ClC_6H_4	**2c** (57) + **6c** (32)
1d	4-FC_6H_4	**2d** (55) + **6d** (30)
1e	4-$CH_3OC_6H_4$	**2e** (54) + **6e** (31)



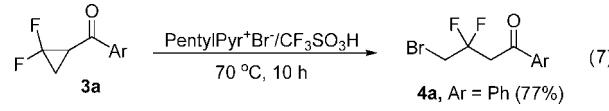
Again, the phenyl-substituted cyclopropyl ketone (**1f**) leads to an alternative outcome as seen in eq 5. In this case, the bromide product (**2f**) becomes the minor product, with the α,β-unsaturated ketone **7** being major, with **7** likely being formed via deprotonation of an intermediate benzylic cation followed by subsequent double-bond isomerization under the acidic conditions.



In order to alleviate the problem of competition in the nucleophilic ring-opening process of the nonfluorinated ketones, triflic acid was used in place of trifluoroacetic acid to create a more bromide-specific ionic liquid reagent. Indeed, this procedure worked to form the bromide products selectively and in excellent yield, as seen in eq 6 and in Table 3. Note that in this case the phenyl-substituted cyclopropyl ketone substrate **1f** is converted mainly to bromide product **2f** (68%), not α,β-unsaturated product **7** (10%), perhaps because of the weaker base properties of triflate versus trifluoroacetate.



When triflic acid is used in the reactions with the *fluorinated* cyclopropyl ketone systems, no advantage is seen in comparison to the results when using trifluoroacetic acid (eq 7, Table 4).



Discussion

The results contained in the above tables indicate that use of the *N*-pentylPyr$^+$Br$^-$/CF_3CO_2H reagent with the fluorinated

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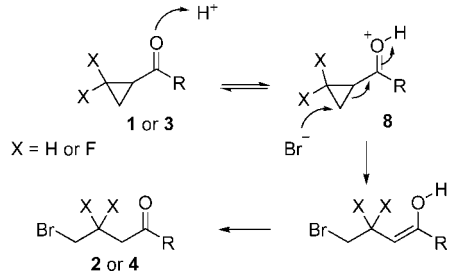
TABLE 3. Reaction of *N*-PentylPyr$^+$Br$^-$/CF_3SO_3H with Nonfluorinated Cyclopropyl Ketones

compd	R	product (%)
1a	CH_3	**2a** (84)
1b	Ph	**2b** (86)
1c	4-ClC_6H_4	**2c** (89)
1d	4-$CH_3C_6H_4$	**2d** (86)
1e	4-$CH_3OC_6H_4$	**2e** (87)

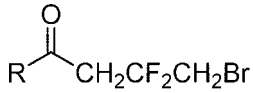
TABLE 4. Reaction of *N*-PentylPyr$^+$Br$^-$/CF_3SO_3H with Fluorinated Cyclopropyl Ketones

compd	product (%)
3a	**4a** (77)
3b	**4b** (74)
3c	**4c** (73)
3d	**4d** (76)
3e	**4e** (78) + **5** (5)

SCHEME 2. Proposed Mechanism



cyclopropyl ketones and the *N*-pentylPyr$^+$Br$^-$/CF_3SO_3H reagent with the nonfluorinated cyclopropyl ketones leads to highly selective, high yield ring-opening reactions to form the respective γ-bromo ketones. In the case of the fluorinated ketones, the synthesis provides the first published route to compounds of the general structure **4**. Such partially fluorinated bromo ketones have the potential to be useful fluorine-containing building blocks.



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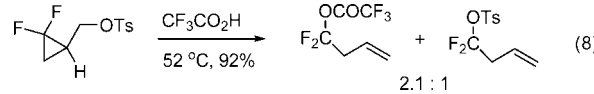
Except for the phenyl-substituted compounds **1f** and **3e**, there can be little doubt that the mechanism of the ring-opening process is S_N2-like in character for both the fluorinated and nonfluorinated ketones, with the process likely involving protonation of the ketone followed by direct nucleophilic attack at the CH_2 group of the cyclopropane (Scheme 2). Intermediate **8** will have cyclopropylcarbinyl cation character and hence exhibit potential electrophilic reactivity at the CH_2 and/or CF_2 sites of the cyclopropane ring. For compounds **1a**−**e**, this will unambiguously lead to S_N2-like nucleophilic attach by bromide at either of the identical CH_2 groups. For **3a**−**d**, an S_N2-like process attack should occur preferentially at the CH_2 position. S_N2 reactions at the RCF_2X sites are almost unheard of, whereas although nucleophilic reactions at RCF_2CH_2X sites are inhibited, they do take place. On the other hand, if a *free cation* (S_N1-like process) were involved, the products should derive from CF_2 attack. There are examples of ring-opening reactions of 2,2-difluorocyclopropylcarbinyl cations, and the regiochemistry of such ring openings is different from the present cases, with nucleophile ending up on the CF_2 carbon as shown by the example in eq 8.[18] Such a result is consistent with the much greater stability of an α,α-difluoro carbocation than a β,β-difluoro carbocation.[19,20]



In the case of the phenyl-substituted cyclopropyl ketones **1f** and **3e**, because of the extra stabilization of the potential benzylic cations it is possible that these reactions proceed by S_N1 processes involving free cations. The formation of the α,β-unsaturated product **7** from **1f** and the furan product **5** from **3e** is more consistent with a carbocation mechanism than one involving the bromides as precursors of **5** and **7**.

The significant difference in selectivity observed in the ring openings of the fluorinated and nonfluorinated systems is consistent with their expected differences in reactivity. The less reactive fluorinated substrates **3a**−**e** should be more selective in their competitive nucleophilic ring-opening processes, with bromide dominating the much less nucleophilic trifluoroacetate ion. The more reactive nonfluorinated substrates **1a**−**f** should be less selective in their choice of nucleophile, and its protonated intermediate **8** should be more cyclopropylcarbinyl cation-like. Triflate, having little nucleophilic character, does not compete with bromide for either type of substrate.

Conclusion

In this paper, we have demonstrated that ionic liquid reagents created by addition of 1 equiv of either CF_3CO_2H or CF_3SO_3H to *N*-pentylpyridinium bromide exhibit excellent chemical reactivities as surrogate HBr reagents in ring-opening reactions of cyclopropyl ketones as well as of 2,2-difluorocyclopropyl ketones to form the respective 3-bromopropyl or 3-bromo-2,2-difluoropropyl ketones in very good to excellent yield. This surrogate HBr reagent is both safer and more effective than the use of fuming aqueous HBr in these reactions with cyclopropyl ketones. In the case of the fluorinated substrates, the reaction, to our knowledge, comprises the first reported synthesis of ketones bearing a 3-bromo-2,2-difluoropropyl group. It is likely that this novel ionic liquid reagent will find many additional applications in synthetic organic chemistry, as would likely their chloride and iodide counterparts.

Experimental Section

Cyclopropyl ketones **1a**−**e** were commercially available, whereas **1f** was obtained as described by Enholm.[21] *N*-Pentylpyridinium bromide was prepared by a variation of the method of Zhu et al.[22] Details of this procedure are provided in the Supporting Information.

Typical Procedure for Preparation of 2,2-Difluorocyclopropyl Ketones 3a−e. Under nitrogen, a mixture of α,β-unsaturated ketone (0.1 mol) and anhydrous sodium fluoride (0.01mol) was heated to 110 °C and stirred for 5 min, and then TFDA ($FSO_2CF_2COOSiMe_3$) (0.2 mol) was added dropwise in 30 min. After addition, the mixture was stirred for further 30 min at 110

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°C. ^{19}F NMR showed all TFDA was consumed. The reaction mixture was cooled to room temperature, and the product was obtained by distillation under reduced pressure.

Characterizations of **3a** and **3b** are provided below, with those of **3c** and **3d** appearing in the Supporting Information.

Phenyl 2,2-Difluorocyclopropyl Ketone, 3a.[23] Prepared starting from precursor 1-phenylprop-2-en-1-one:[15] liquid, 49%; ^{1}H NMR δ 1.74−1.86 (m, 1H), 2.37−2.48 (m, 1H), 3.35−3.45 (m, 1H), 7.46−7.53 (m, 2H), 7.59−7.64 (m, 1H), 7.99−8.02 (m, 2H); ^{19}F NMR, δ −124.4 to −125.1 (m, 1F), −140.3 to-140.9 (m, 1F).

4-Chlorophenyl 2,2-Difluorocyclopropyl Ketone, 3b. Prepared starting from precursor 1-(4-chlorophenyl)prop-2-en-1-one:[24] solid, 47%; mp 47−48 °C; ^{1}H NMR δ 1.76−1.88 (m, 1H), 2.36−2.48 (m, 1H), 3.29−3.39 (m, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.94 (d, J = 8.7 Hz, 2H); ^{19}F NMR δ −124.3 to −124.9 (m, 1F), −140.2 to −140.7 (m, 1F); ^{13}C NMR, δ 16.0 (t, J = 10 Hz), 29.9 (t, J = 11 Hz), 111.7 (q, J = 289 Hz), 129.4, 130.0, 135.5, 140.5, 189.6; HRMS (EI) calcd for $C_{10}H_8ClF_2O$ [M + H]$^+$ 217.0232, found 217.0241. Anal. Calcd for $C_{10}H_7ClF_2O$: C, 55.45; H, 3.26. Found: C, 55.15; H, 3.23.

Typical Procedure for the Reaction of the Cyclopropyl Ketones with the Ionic Liquid Reagents. Under nitrogen, into a 25 mL round-bottomed flask with stirbar was placed *N*-pentylpyridinium bromide (2.30 g, 10 mmol), which was heated to 70 °C until the salt melted, and then either trifluoroactic acid or triflic acid (10 mmol) was added through a syringe. The mixture was then stirred at 70 °C for 5 min and cooled to room temperature, at which time it was still a liquid. Substrate (5mmol) was added in one portion and then stirred at 70 °C for 10 h. The reaction mixture was cooled to room temperature, extracted with ethyl ether, washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent, the products **2a**−**f**, **6a**−**e**, **7**, **4a**−**e**, and **5** were isolated by column chromatography, eluting with 10:1 to 5:1 hexane/ethyl acetate.

Characterization data are provided below for **2a**,**b**, **6a**,**b**, and **4a**,**b** with the data for the remaining compounds appearing in the Supporting Information.

5-Bromo-2-pentanone (2a):[25] ^{1}H NMR δ 2.09 (q, J = 7.2 Hz, 2H), 2.16 (s, 3H), 2.63 (t, J = 6.9 Hz, 2H), 3.42 (t, J = 6.6 Hz, 2H).

5-Trifluoroacetoxy-2-pentanone (6a): ^{1}H NMR δ 2.03 (q, J = 6.6 Hz, 2H), 2.21 (s, 3H), 2.61 (t, J = 7.2 Hz, 2H), 4.36 (t, J = 6.0 Hz, 2H); ^{19}F NMR δ −75.6 (s, 3F); ^{13}C NMR, δ 22.3, 30.0, 39.2, 67.5, 114.7 (q, J = 286 Hz), 157.6 (q, J = 42 Hz), 207.0; HRMS (EI) calcd for $C_7H_{10}F_3O_3$ [M + H]$^+$ 199.0582, found 199.0577. Anal. Calcd for $C_{10}H_9F_3O_3$: C, 42.43; H, 4.58. Found: C, 42.54; H, 4.62.

1-Phenyl-4-bromo-1-butanone (2b):[26] ^{1}H NMR δ 2.31 (q, J = 6.6 Hz, 2H), 3.19 (t, J = 6.9 Hz, 2H), 3.55 (t, J = 6.3 Hz, 2H), 7.45−7.60 (m, 3H), 7.96−7.99 (m, 2H).

1-Phenyl-4-trifluoroacetoxy-1-butanone (6b): ^{1}H NMR δ 2.22 (q, J = 6.6 Hz, 2H), 3.12 (t, J = 6.9 Hz, 2H), 4.47 (t, J = 6.3 Hz, 2H), 7.45−7.59 (m, 3H), 7.96−7.99 (m, 2H); ^{19}F NMR δ −75.4 (s, 3F); ^{13}C NMR δ 22.8, 34.3, 67.7, 114.7 (q, J = 286 Hz), 128.2, 128.9, 133.6, 136.7, 157.7 (q, J = 42 Hz), 198.6; HRMS (EI) calcd for $C_{12}H_{12}F_3O_3$ [M + H]$^+$ 261.0739, found 261.0733. Anal. Calcd for $C_{12}H_{11}F_3O_3$: C, 55.39; H, 4.26. Found: C, 55.66; H, 4.36.

4-Bromo-3,3-difluoro-1-phenyl-1-butanone (4a): ^{1}H NMR δ 3.82 (t, J = 12.7 Hz, 2H), 3.95 (t, J = 12.7 Hz, 2H), 7.48−7.54 (m, 2H), 7.60−7.65 (m, 1H), 7.94−7.97 (m, 2H); ^{19}F NMR δ −93.1 (q, J = 12.4 Hz, 2F); ^{13}C NMR δ 31.4 (t, J = 32 Hz), 42.6 (t, J = 26 Hz), 120.2 (t, J = 244 Hz), 128.5, 129.1, 134.3, 136.4, 193.1 (t, J = 6.0 Hz); HRMS (EI) calcd for $C_{10}H_{10}BrF_2O$ [M + H]$^+$ 262.9883, found 262.9886. Anal. Calcd for $C_{10}H_9BrF_2O$: C, 45.65; H, 3.46. Found: C, 45.98; H, 3.47.

4-Bromo-3,3-difluoro-1-(4-chlorophenyl)-1-butanone (4b): ^{1}H NMR δ 3.78 (t, J = 13.5 Hz, 2H), 3.92 (t, J = 13.5 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H); ^{19}F NMR δ −93.1 (q, J = 12.4 Hz, 2F); ^{13}C NMR δ 31.2 (t, J = 32 Hz), 42.6 (t, J = 26 Hz), 120.1 (t, J = 244 Hz), 129.5, 129.9, 134.8, 140.9, 192.0 (t, J = 6.0 Hz); HRMS (EI) calcd for $C_{10}H_9BrClF_2O$ [M + H]$^+$ 296.9493, found 296.9512. Anal. Calcd for $C_{10}H_8BrClF_2O$: C, 40.37; H, 2.71. Found: C, 40.77; H, 2.65.

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Supporting Information Available: Proton, carbon, and fluorine NMR spectra of all new compounds, as well as proton spectra of previously reported compounds **1f**, **2a**−**f**, **3a**,**e**, **5**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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