Trifluoromethanesulfonic Anhydride-Promoted α-Bromination of Ketones with Grignard Reagent or Magnesium Bromide

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The direct α-bromination of various ketones using trifluoromethanesulfonic anhydride and Grignard reagent or magnesium bromide in ether gave the corresponding α-bromo ketones in moderate to good yields under mild reaction conditions.

Key words trifluoromethanesulfonic anhydride; α-bromo ketones; α-bromo-α,β-enones

Halogenation of ketones has been widely reported in organic syntheses. Therefore, a number of methods have been developed for this purpose. Classical methods for the bromination of ketones include the use of molecular bromine[1] and copper(II) bromide.[2] Halogenation is characterized by selectivity at the α-carbon of the ketones in the side favorable to enolization. Therefore, the reaction is carried out in the presence of acid to increase the rate of halogenation. Under these acidic conditions, α-chlorination of an unsymmetrical ketone takes place at the more highly substituted α-carbon atom.[3] To effect the α-chlorination of a ketone at the less substituted carbon, several methods have been studied, including the initial formation of the kinetic enolate of a ketone[4] and the bromination of enol trimethylsilyl ethers.[5]

Selective bromination of ketones at the α-position in the presence of a double bond has been achieved through the action of phenyltrimethylammonium tribromide,[6] cupric bromide,[7] and pyrrolidine hydrotribromide.[8] Other methods reported for the preparations of α-halo ketones include sulfonyl chloride,[4] 2-bromo-2-cyano-*N*,*N*-dimethylacetamide,[9] and sulfuryl chloride.[10] Recently, Righi and co-workers have reported the selective transformation of cyclic enones into α-halo-α,β-enones using dimethyldioxirane and metal halides/Amberlyst.[11]

We have recently reported a new simple procedure for the homo-coupling reaction of Grignard reagents using trifluoromethanesulfonic anhydride (Tf_2O).[12] On the other hand, Kotsuki has reported a strange reaction in which a triflate reacts with methylmagnesium iodide in the presence of copper(I) bromide to give the corresponding iodinated product in 54% yield.[13] From these results, we envisaged that new brominating reagents could be developed by using Tf_2O and Grignard reagents.

In this paper, we describe a convenient synthesis of α-bromo ketones from the corresponding ketones using Tf_2O and Grignard reagent or $MgBr_2$. The scope and limitations of this procedure are also discussed.

Results and Discussion

In an effort to arrive at the optimun reaction conditions for the bromination, different reaction conditions (addition order of ketone, solvent and brominating reagent) were varied for the bromination of cyclohexanone. Method A: Tf_2O was added over a few minutes to a stirred CH_2Cl_2 or ether solution of cyclohexanone kept at 0 °C under a balloon of nitrogen. After 1 h, methylmagnesium bromide (MeMgBr) was added, and the mixture was stirred for 6 h at room temperature. Method B: A mixture of Tf_2O and brominating reagent in CH_2Cl_2 or ether was stirred under a balloon of nitrogen. After 10 min, cyclohexanone was added to the mixture.

Table 1 summarizes the results of the α-bromination of cyclohexanone under various reaction conditions. When cyclohexanone was treated with MeMgBr in the presence of Tf_2O in CH_2Cl_2 in method A, a low yield of 2-bromocyclohexanone was obtained (10%); the major product of the reaction was 1-cyclohexenyl triflate (41%, entry 1).[14] The solvent was critical to the success of this reaction. Thus, the reaction in ether in place of CH_2Cl_2 proceeded much more smoothly, giving the 2-bromocyclohexanone in a yield of 53% (entry 2). However, the reaction of cyclohexanone with MeMgBr/Tf_2O in ether (method B) gave 2-bromocyclohexanone in 92% yield within 10 min at 0 °C (entry 3). A stoichiometric amount of Tf_2O was necessary for the reaction. After treatment of cyclohexanone with 0.5 and 0.2 eq of Tf_2O, the yields of 2-bromocyclohexanone decreased to 44 and 6%, respectively (entries 4, 5). In place of ether the use of CH_2Cl_2 gave only 2-bromocyclohexanone in 3% yield and unreacted cyclohexanone in 97% yield, even when the reaction was carried out at room temperature for 1 h (entry 6). On the other hand, treatment of cyclohexanone with phenylmagnesium bromide (PhMgBr) gave 2-bromocyclohexanone in 33% yield along with biphenyl (entry 7).[12]

Many authors have reported that the Grignard reagent in solution either consists in part of a dimeric species or contains a mixture of dialkylmagnesium and MgX_2.[15,16] Therefore, we attempted to brominate cyclohexanone using $MgBr_2$ in the presence of Tf_2O. In the first example, the treatment of cyclohexanone in ether with 1.1 eq of $MgBr_2$ and 0.5 eq of Tf_2O at 0 °C for 10 min gave 2-bromocyclohexanone in 92% yield (entry 8). The use of 0.5 eq of $MgBr_2$ and 0.5 eq of Tf_2O resulted in a lower yield of 2-bromocyclohexanone. Attempts to effect the bromination of cyclohexanone using CH_2Cl_2 resulted in a low yield (entry 10). Unfortunately, in the case of a chlorination of cyclohexanone with $Tf_2O/MgCl_2$ in ether, no chlorination product is obtained, and only the starting cyclohexanone was recovered (entry 11).

In order to show the efficiency of method B in ether, we extended the reaction to other substrates and explored the generality of the reaction. As shown in Table 2, the reaction of acetophenone with 1.1 eq of $MgBr_2$ and 0.5 eq of Tf_2O at 0 °C gave α-bromoacetophenone in 79% yield (entry 2). The reaction was completed in 10 min. On the other hand, treat-

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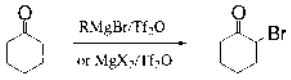
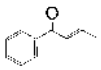
Table 1. α-Bromination of Cyclohexanone with Tf_2O and Grignard Reagents or MgX_2



Entry	Solvent	Method	Halogenating reagent (eq)	Tf_2O eq	Reaction temp °C	Reaction time	Yield[a] (%)
1	CH_2Cl_2	A	MeMgBr (1.5)	1.5	r.t.	6 h	10[b]
2	Et_2O	A	MeMgBr (1.5)	1.5	r.t.	6 h	53
3	Et_2O	B	MeMgBr (1.0)	1.2	0	10 min	92
4	Et_2O	B	MeMgBr (1.0)	0.5	0	10 min	44
5	Et_2O	B	MeMgBr (1.0)	0.2	0	10 min	6
6	CH_2Cl_2	B	MeMgBr (1.0)	1.2	r.t.	1 h	3
7	Et_2O	B	PhMgBr (1.0)	1.2	0	10 min	33[c]
8	Et_2O	B	$MgBr_2$ (1.1)	0.5	0	10 min	92 (89)
9	Et_2O	B	$MgBr_2$ (0.5)	0.5	0	10 min	50
10	CH_2Cl_2	B	$MgBr_2$ (1.1)	0.5	0	10 min	11
11	Et_2O	B	$MgCl_2$ (1.1)	0.5	0	10 min	0[d]
12	Et_2O	B	$MgBr_2$ (1.1)	—	0	20 min	0[d]

a) Determined by GLC analysis. Value in parenthesis indicates yield after purification. *b*) The major product is 1-cyclohexenyl triflate (41%). *c*) A small amount of biphenyl (6%) was produced. *d*) No reaction occurred; only starting materials remained according to GLC.

Table 2. Bromination of Ketones with Tf_2O and MeMgBr or $MgBr_2$

Entry	Substrate	Brominating reagent (eq)	Tf_2O eq	Reaction temp °C	Reaction time	Yield[a] (%)
1		MeMgBr (1.2)	1.2	r. t.	3 h	74
2		$MgBr_2$ (1.1)	0.5	0	10 min	79
3		MeMgBr (2.0)	2.4	r. t.	10 min	85
4		$MgBr_2$ (1.1)	0.5	0	10 min	79
5		MeMgBr (1.0)	1.2	r. t.	4 h	88
6		$MgBr_2$ (1.1)	0.5	0	10 min	91
7		MeMgBr (2.0)	2.4	30	2 h	84
8		$MgBr_2$ (1.1)	0.5	0	10 min	77
9		MeMgBr (1.2)	2.4	r. t.	40 h	20[b] (25)[c]
10		$MgBr_2$ (1.1)	0.5	0	10 min	92[b] (98)[c]
11		$MgBr_2$ (1.1)	0.5	r. t.	10 min	80[b] (86)[c]
12		$MgBr_2$ (1.1)	0.5	r. t.	10 min	80[b] (82)[c]
13		$MgBr_2$ (1.1)	—	r. t.	20 min	0[d]
14		$MgBr_2$ (1.1)	0.5	r. t.	10 min	82[e]

a) Isolated yields. *b*) Isolated yields of α-bromo-α,β-enones. *c*) Values in parentheses indicate GLC yield of crude α,β-dibromo ketones. These compounds are unstable. *d*) No reaction occurred; only starting materials remained according to GLC. *e*) Yield of 1,2-dibromocyclohexane.

ment with MeMgBr as a brominating reagent was less effective, and the reaction required longer reaction times and a higher temperature to attain a comparable yield (entry 1). The treatment of cycloheptanone or 4-heptanone with Tf_2O/MeMgBr or $Tf_2O/MgBr_2$ afforded the corresponding α-bromo ketones in a good yield (entries 3—6).

The substituent effects in the α-position of ketone on the α-bromination were also examined. The bromination of 2-methylcyclohexanone with MeMgBr or $MgBr_2$ in the presence of Tf_2O provided 2-bromo-2-methylcyclohexanone in 84 and 77% yields, respectively. In each case, 2-bromo-6-methylcyclohexanone was formed in 6 and 9% yields.

Entries 9—12 show the results for the bromination of α,β-enones. The treatment of 2-cyclohexen-1-one with $MgBr_2$/Tf_2O afforded 2,3-dibromocyclohexanone (entry 10). Separation by alumina chromatography resulted in 2-bromo-2-cyclohexen-1-one obtained by dehydrobromination in 92% yield. α,β-Dibromo ketones showed a strong tendency to decompose and were not isolated in analytically pure forms. In most cases, the α,β-dibromo ketones were fairly pure; their structures were determined unambiguously by spectral methods. A similar dehydrobromination has been observed for the bromination of α,β-enones with bromine[17] and oxone (2

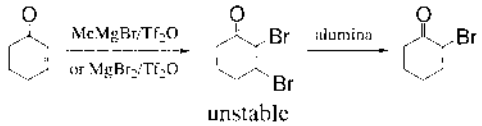


Chart 1

$KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$/NaBr).[18] On the other hand, bromination with MeMgBr/Tf_2O was less effective than with $MgBr_2$/Tf_2O for the formation of α-bromo-α,β-enones (entry 9).

In order to determine the active species of the present method, we examined the bromination of simple alkene with the two methods (entries 13, 14). Cyclohexene afforded excellent yields of the 1,2-dibromocyclohexane upon treatment with $MgBr_2$/Tf_2O. Direct treatment of cyclohexene with $MgBr_2$ without Tf_2O did not afford any 1,2-dibromocyclohexane. The addition of Br_2 to cyclohexene suggests that this combination of $MgBr_2$/Tf_2O provides an *in situ* generation of Br_2.

Finally, we examined the addition of Br_2 alone to ketone. The reaction of cyclohexanone in ether with 1.1 eq of Br_2 in $CHCl_3$ at 0 °C for 10 min gave 2-bromocyclohexanone and dibrominated cyclohexanone as a 1 : 2 mixture.

Conclusion

We have described a new procedure for the bromination of ketones in a regioselective fashion by reaction of Tf_2O with MeMgBr or $MgBr_2$ followed by addition of the ketone. The bromination occurs at the more substituted carbon atom of an unsymmetrical ketone and yields are good. The procedure can also be used to convert α,β-enones into α-bromo-α,β-enones by addition of Br_2 followed by elimination of HBr.

The mechanism of this reaction is not yet understood. The addition of Br_2 to cyclohexene suggests that the combination of MeMgBr/Tf_2O or $MgBr_2$/Tf_2O reagents provides an *in situ* generation of Br_2. Further studies towards identifying the actual reactive species of this bromination reaction of ketones are under current investigation.

Experimental

General Methods NMR spectra were recorded in $CDCl_3$ on a JEOL GSX-400 spectrometer operating at 400 and 100 MHz for ^1H and ^{13}C, respectively. Chemical shifts for NMR spectra were referenced to internal $(CH_3)_4Si$. Mass spectra were measured with a Perkin-Elmer model 910 spectrometer operating in the electron impact mode (70 eV). IR spectra were recorded on a Perkin-Elmer model 1600 spectrophotometer. Gas chromatography was carried out on a 20 m×0.22 mm capillary column packed with methyl silicone.

General Procedure To a solution of $MgBr_2 \cdot Et_2O$ (1.1 mmol) in 5 ml of dry ether was added Tf_2O (0.5 mmol) under stirring at 0 °C. The clear solution immediately turned yellow-orange. After stirring at 0 °C for 10 min, cycloheptanone (1 mmol) was slowly added in 5 ml of dry ether and further stirred for 10 min at 0 °C. The reaction was quenched with water and the organic portion was extracted with ether, washed with $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give a light yellow oil, and the crude oil was purified by preparative TLC (alumina, ether : hexane = 1 : 1) to yield 2-bromocycloheptanone (0.15 g, 79%).[19] ^1H-NMR δ: 1.33—1.43 (m, 1H), 1.51—1.63 (m, 2H), 1.72—1.81 (m, 1H), 1.91—2.06 (m, 3H), 2.33—2.41 (m, 1H), 2.47—2.53 (m, 1H), 4.38 (dd, J=9.5, 5.1 Hz, 1H); ^{13}C-NMR δ: 25.0, 26.8, 29.6, 34.3, 39.4, 53.7, 206.2; *m/z* (rel. intensity): 192 (M^+, 7), 190 (M^+, 7), 112 (12), 111 (74), 93 (22), 84 (44), 83 (66), 69 (35), 67 (35), 56 (33), 55 (100).

2-Bromocyclohexanone[9,19] Pale yellow oil. ^1H-NMR δ: 1.70—1.78 (m, 1H), 1.80—1.88 (m, 1H), 1.91—2.08 (m, 2H), 2.18—2.27 (m, 1H), 2.30—2.38 (m, 2H), 2.93—3.01 (m, 1H), 4.44—4.48 (m, 1H); ^{13}C-NMR δ: 22.2, 26.8, 36.8, 38.0, 53.5, 203.4; MS *m/z* (rel. intensity): 178 (M^+, 11), 176 (M^+, 11), 134 (9), 132 (9), 97 (62), 69 (46), 55 (100).

2-Bromoacetophenone[9] mp 49.2—50.6 °C. ^1H-NMR δ: 4.48 (s, 2H), 7.46—7.50 (m, 2H), 7.58—7.61 (m, 1H), 7.96—7.98 (m, 2H); ^{13}C-NMR δ: 31.1, 128.8, 128.9, 133.9, 191.2; MS *m/z* (rel. intensity): 200 (M^+, 3), 198 (M^+, 3), 106 (8), 105 (100), 91 (10), 77 (48).

3-Bromo-4-heptanone[20] Pale yellow oil. ^1H-NMR δ: 0.94 (t, J=7.3 Hz, 3H), 1.02 (t, J=7.3 Hz, 3H), 1.61—1.70 (m, 2H), 1.91—2.00 (m, 1H), 2.00—2.08 (m, 1H), 2.57—2.74 (m, 2H), 4.19 (dd, J=8.1, 6.6 Hz, 1H); ^{13}C-NMR δ: 12.0, 13.6, 17.4, 26.9, 40.9, 55.5, 204.2; MS *m/z* (rel. intensity): 71 (89), 55 (13), 43 (100).

2-Bromo-2-methylcyclohexanone[5] Pale yellow oil. ^1H-NMR δ: 1.57—1.65 (m, 1H), 1.75—1.81 (m, 2H), 1.82 (s, 3H), 2.03—2.10 (m, 2H), 2.33—2.41 (m, 2H), 3.17—3.26 (m, 1H); ^{13}C-NMR δ: 22.3, 26.8, 28.1, 36.7, 43.6, 65.8, 204.6; MS *m/z* (rel. intensity): 192 (M^+, 3), 190 (M^+, 3), 148 (13), 146 (13), 111 (20), 83 (17), 69 (10), 67 (22), 55 (100).

2,3-Dibromocyclohexanone[21] Pale yellow oil. ^1H-NMR δ: 1.65—2.07 (m, 1H), 2.08—2.11 (m, 1H), 2.23—2.41 (m, 2H), 2.62—2.72 (m, 1H), 3.04—3.13 (m, 1H), 4.50—4.51 (m, 1H), 4.72—4.75 (m, 1H); ^{13}C-NMR δ: 21.5, 27.2, 35.1, 50.6, 53.1, 200.6; MS *m/z* (rel. intensity): 177 (53), 175 (55), 121 (16), 119 (16), 95 (19), 66 (63), 67 (100).

2-Bromo-2-cyclohexen-1-one[22] mp 75.2—76.1 °C. ^1H-NMR δ: 2.06—2.12 (m, 2H), 2.46—2.50 (m, 2H), 2.61—2.65 (m, 2H), 7.45 (t, J=4.8 Hz, 1H); ^{13}C-NMR δ: 22.7, 28.4, 38.4, 123.8, 151.3, 191.2; MS *m/z* (rel. intensity): 176 (M^+, 31), 174 (M^+, 33), 148 (33), 146 (33), 135 (9), 133 (10), 68 (9), 67 (67), 55 (44), 41 (27), 39 (100).

3,4-Dibromo-2-heptanone Pale yellow oil. ^1H-NMR δ: 0.98 (t, J=7.3 Hz, 3H), 1.48—1.56 (m, 1H), 1.60—1.72 (m, 1H), 1.77—1.87 (m, 1H), 2.17—2.25 (m, 1H), 2.37 (s, 3H), 4.34—4.39 (m, 1H), 4.50 (d, J=11.0 Hz, 1H); ^{13}C-NMR δ: 13.3, 19.6, 26.5, 37.4, 51.5, 54.2, 198.5; MS *m/z* (rel. intensity): 150 (25), 148 (25), 121 (6), 119 (6), 97 (11), 93 (5), 70 (6), 69 (100).

3-Bromo-3-hepten-2-one Pale yellow oil. ^1H-NMR δ: 0.93 (t, J=7.3 z, 3H), 1.53—1.62 (m, 2H), 2.37—2.45 (m, 2H), 2.46 (s, 3H), 7.16 (t, J=7.0 Hz, 1H); ^{13}C-NMR δ: 13.9, 21.1, 26.5, 34.6, 127.7, 145.9, 191.8; MS *m/z* (rel. intensity): 192 (M^+, 60), 190 (M^+, 61), 177 (52), 175 (53), 151 (61), 149 (62), 135 (28), 133 (29), 111 (36), 96 (41), 95 (44), 82 (23), 69 (20), 67 (50), 55 (19), 53 (41), 43 (100); IR (neat, cm^{-1}): 2960, 2928, 2896, 1686, 1617, 1609, 1458, 1357, 1242, 1214; *Anal*. Calcd. for $C_7H_{11}OBr$: C 44.00, H 5.80; found: C 44.28, H 5.74.

2,3-Dibromo-1-phenyl-1-butanone[23] Pale yellow oil. ^1H-NMR δ: 2.01 (d, J=7.0 z, 3H), 4.73—4.77 (m, 1H), 5.40 (d, J=10.6 Hz, 1H), 7.47—7.51 (m, 2H), 7.59—7.63 (m, 1H), 8.01—8.02 (m, 2H); ^{13}C-NMR δ: 24.3, 44.9, 128.8, 128.9, 133.9, 191.3; MS *m/z* (rel. intensity): 106 (8), 105 (100), 77 (31).

2-Bromo-1-phenyl-2-buten-1-one[24] Pale yellow oil. ^1H-NMR δ: 2.05 (d, J=7.0 Hz, 3H), 6.91 (q, J=7.0 Hz, 1H), 7.41—7.68 (m, 5H); ^{13}C-NMR δ: 18.4, 128.4, 129.5, 132.4, 136.7, 143.6, 190.5; MS *m/z* (rel. intensity): 226 (M^+, 7), 224 (M^+, 7), 145 (29), 104 (8), 105 (100), 77 (51).

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