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Preparation of α-Haloacrylate Derivatives via Dimethyl Sulfoxide-Mediated Selective Dehydrohalogenation

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ABSTRACT

R = H, Alkyl; X = Br, Cl
Y = COOMe, COOH, CN, CHO, Ketone

Dimethyl sulfoxide causes α,β-dihalopropanoate derivatives to undergo efficient, selective dehydrohalogenation to form α-haloacrylate analogues. A variety of α-halo Michael acceptors were prepared in dimethyl sulfoxide under mild, base-free conditions, including the preparation of α-bromoacrolein and α-chloro- and bromoacrylonitriles. Synthesis of these molecules has been reported in the literature to be difficult. Among all the existing dehydrohalogenation procedures, this protocol is the most facile, practical, and environmentally benign process.

Recent reports on new methods for the preparation of α-haloacrylates reflect the renewed interest in the synthesis of these useful building blocks[1] and prompted the submission of this communication. Acrylate derivatives are not only used as Michael acceptors,[2] but are also frequently employed as dienophiles or dipolarophiles in cycloaddition reactions.[3] With an additional vinyl halogen atom at the α-position to the carbonyl, it is not surprising that α-haloacrylate analogues have found more synthetic application due to this added functional handle. For example, β,γ-unsaturated esters and lactones can be easily obtained by reaction of the α-haloacrylate analogues with dialkyl phosphonates,[4] and vinyloxiranes can be prepared through reaction of aldehydes with lithium dienolates.[5] The halogen atom could also readily undergo metal−halogen exchange,[6] allowing for homologation of the parent structure through C-alkylation. The α-haloacrylate analogues not only increase their utility as Michael acceptors[7] or dienophiles in cycloaddition chemistry,[8] but they can also serve as the functionalized vinyl halide in transition metal-mediated coupling reactions.[9] With the

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(3) Chang, M.; Hsu, R.; Tseng, T.; Sun, P.; Chang, N. *Tetrahedron* **2004**, *60*, 5545.

(4) Hirao, T.; Fujihara, Y.; Kurokawa, K.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1986**, *51*, 2830.

(5) Hudlicky, T.; Fleming, A.; Lovelace, T. C. *Tetrahedron* **1989**, *45*, 3021.

(6) (a) Grossman, G.; Poncioni, M.; Bornand, M.; Jolivet, B.; Neuburger, M.; Sequin, U. *Tetrahedron* **2003**, *59*, 3237. (b) Thibonnet, J.; Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787.

(7) Selected examples: (a) Saoudi, A.; Hamelin, J.; Benhaoua, H. *J. Chem. Res. Synop.* **1996**, *11*, 491. (b) Chen, C.; Xi, C.; Jiang Y.; Hong, X. *Tetrahedron Lett.* **2004**, *45*, 6067. (c) Gutke, H.; Braun, N. A.; Spitzner, D. *Tetrahedron* **2004**, *60*, 8137. (d) Prostenic, M.; Salzman, N. P.; Carter, H. E. *J. Am. Chem. Soc.* **1955**, *77*, 1856. (e) Martin, A. R.; Caputo, J. F. *J. Org. Chem.* **1974**, *39*, 1811. (f) Martin, A. R.; Mallick, S. K.; Caputo, J. F. *J. Org. Chem.* **1974**, *39*, 1808.

(8) (a) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. (b) Zhou, G.; Hu, Q.; Corey, E. J. *Or. Lett.* **2003**, *5*, 3979. (c) Sun, P.; Chang, M.; Chiang M.; Chang, N. *Org. Lett.* **2003**, *5*, 1761.

(9) Selected references: (a) Bellur, E.; Langer, P. *Eur. J. Org. Chem.* **2005**, *22*, 4815. (b) Sorg, A.; Blank, F.; Brueckner, R. *Synlett* **2005**, *8*, 1286. (c) Majo, V. J.; Prabhakaran, J.; Simpson, N. R.; Van Heertum, R. L.; Mann, J. J.; Kumar, J. S. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4268.

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rapidly increasing application of such coupling reactions in synthetic and medicinal chemistry,[10] alternate synthetic methods for these building blocks are of constant interest. The existing synthetic procedures in the literature are often associated with complicated operations and lack of generality.[11] This is true especially for the preparation of α-bromo acrolein derivatives due to the high reactivity of the aldehyde. Here we report a set of new general synthetic procedures for the preparation of a variety of such derivatives conveniently via dimethyl sulfoxide (DMSO)-mediated dehydrohalogenation from the α,*β*-dihalo precursors with high yields (Scheme 1).

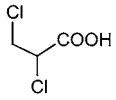
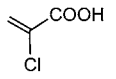
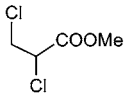
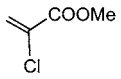
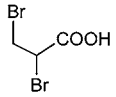
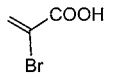
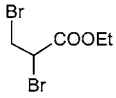
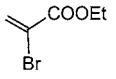
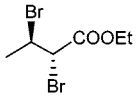
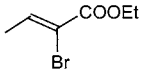
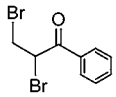
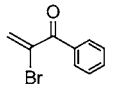
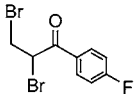
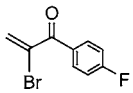
Scheme 1. Formation of α-Bromoacrylates in DMSO

We have recently reported that sulfoxides convert α,α-dihalomethylarenes to the corresponding aldehydes[12] through oxygen transfer from the sulfoxide to the *gem*-dihalo compounds. We were interested to see if subjection of the α,*β*-dihalo substrates to DMSO under similar conditions would provide new synthetic applications. Thus, a variety of α,*β*-dihalo compounds were treated with DMSO and very interesting results were obtained. We have previously reported that the 1,2-*di-activated* dihalopropanoates (R = phenyl), upon heating in DMSO, undergo reductive debromination to generate the corresponding olefin.[13] Herein, we communicate further that the *mono-activated* analogues (R = H, Alkyl, Scheme 1) prefer the dehydrohalogenation pathway, leading to the exclusive formation of α-haloacrylate derivatives. No reductive dehalogenation byproducts were observed.

Table 1 lists the representative examples and reaction conditions. Most of the *vic*-dihalo starting materials in the table are commercially available, or could be prepared conveniently from the corresponding acrylate precursors through known olefin halogenation reactions.[14] Although the reaction occurs in neat DMSO, it was observed that addition of trace amounts of water (~5%) accelerated the reaction.

The conversion of the α,*β*-dihalo substrates to α-haloacrylate derivatives in DMSO proceeded smoothly, and both α,*β*-dichloro and dibromo precursors underwent dehydrohalogenation to give the corresponding α-haloacrylates in excellent yields. The dichloro analogues (entries 1 and 2, Table 1) appear to be less reactive than the corresponding bromo counterparts (entries 3 and 4) as they required higher reaction temperatures or longer reaction times. The acids have similar reactivity to the corresponding esters. In the case of a substituent at the C-3 carbon (entry 5), the reaction afforded the (*Z*)-ethyl 2-bromobut-2-enoate in high yield (91%). The geometry of the double bond was established through NMR experiments and is in agreement with the literature.[15] The α,*β*-dibromoketones (entries 6 and 7) afforded the α-bromovinylketones in good yield under similar conditions.

Table 1. Formation of α-Haloacrylates in DMSO

entry	S.M.	product	conditions	yield
1			120 °C 6 h	90%
2			120 °C 6 h	91%
3			75 °C 8 h	94%
4			75 °C 8 h	89%
5			75 °C 7 h	91%
6			75 °C 12 h	92%
7			80 °C 12 h	75%

The procedure employed a steam-distillation and afforded the α-bromoacrolein in low yield. Due to the

We further extended our investigation to the formation of α-bromo acrolein analogues. Although the α-bromo acrolein moiety possesses three diverse functional groups for which many types of transformations can be envisioned, its synthetic application can only be found scattered in the literature due to lack of proper synthetic procedures, especially for the small aliphatic acrolein molecules. For example, the literature protocols for the preparation of α-bromoacrolein (entry 1 of Table 2) were very limited, and the one most frenquently cited was published more than a half century ago.[16]

(10) (a) Romagnoli, R.; Baraldi, P. G.; Tabrizi, M. A.; Bermejo, J.; Estevez, F.; Borgatti, M.; Gambari, R. *J. Med. Chem.* **2005**, *48*, 7906. (b) Beria, I.; Baraldi, P. G.; Cozzi, P.; Caldarelli, M.; Geroni, C.; Marchini, S.; Mongelli, N.; Romagnoli, R. *J. Med. Chem.* **2004**, *47*, 2611.

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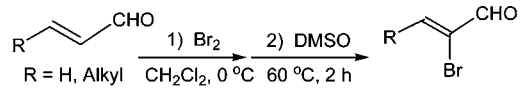
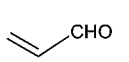
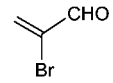
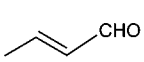
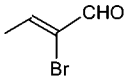
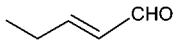
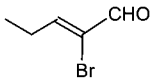
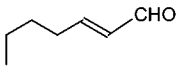
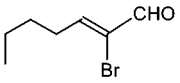
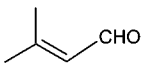
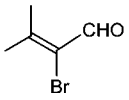
(13) Li, W.; Li, J.; Lin, M.; Wacharasindhu, S.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 6016.

(14) (a) Johnson, J. R.; McEwen, W. L. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 521. (b) Snyder, H. R.; Brooks, L. A. *Organic Syntheses*; Wiley: New York, 1943; Vol. II, p 171.

(15) Chang, M.; Hsu, R.; Tseng, T.; Sun, P.; Chang, N. *Tetrahedron* **2004**, *60*, 5545.

Table 2. Formation of the α-Haloacroleins



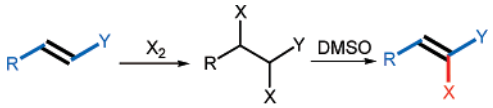
entry	S.M.	product	yield
1			85%
2			91%
3			92%
4			94%
5			95%

unavailability and instability of the starting α,*β*-dibromopropionaldehyde, we tested the generality of the DMSO procedure for the preparation of this class of compounds starting from the bromination of the commercially available acrolein and other aliphatic acrolein analogues and then treated the crude dibromo intermediate with DMSO at 60 °C. Extraction of the reaction mixture with pentane after addition of water provided the desired aldehydes. The two-step consecutive operation is simple and gives the desired α-bromoacrolein analogues in 85−95% yield (Table 2). The resulting products were clean and could be used without further purification.

For *β*-monosubstituted enals (entries 2, 3, and 4 of Table 2), the starting olefin favors the *E*-configuration. It was confirmed by NMR that the α-brominated products have *Z*-configuration after the consecutive bromination−dehydrobromination pathway. This reaction outcome indicates that the original trans-relationship of the alkyl and the aldehyde with respect to the double bond is retained. The mild reaction conditions also allowed for the preparation of 2-bromo-3-methylbutenal with high yield (entry 5 of Table 2). Synthesis of this compound has been found to be difficult in the literature, requiring a sophisticated procedure and resulting in low yield.[17]

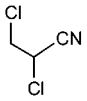
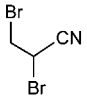
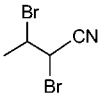
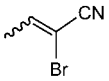
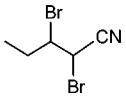
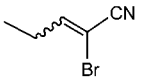
The process here accomplished a net result of α-bromination of the acrylate analogues with retention of the original olefin configuration as shown in Scheme 2.

Scheme 2



We further expanded our investigations to the preparation of α-haloacrylonitriles from their corresponding *vic*-dihalo precursors (Table 3). The reaction proceeded very smoothly

Table 3. Formation of the α-Haloacrylonitriles

entry	S.M.	product	neat DMSO (yield)
1			80 °C, 24 h (86%)
2			80 °C, 1 h (94%)
3			80 °C, 1 h 90% *E*:*Z* = 1:1.3
4			80 °C, 1 h 86% *E*:*Z* = 1:1.6

at 80 °C with excellent yields. When the reaction progress was monitored by ^{1}H NMR in DMSO-d_6, a clean spectrum was obtained showing only the conversion of the starting material to product. Again, both dichloro and dibromo precursors afforded the desired products. The *vic*-dichloride is less reactive than the corresponding bromide, similar to the trend observed in Table 1. It was also observed that the dehydrohalogenation was less stereoselective (entries 3 and 4 of Table 3) when there was a *β*-substitution. In these cases, a mixture of *E*/*Z* isomers was obtained.

It should be pointed out that prior reports on the preparation of α-halo acrylonitriles were limited, featuring quite involved procedures to avoid competing radical polymerization (reaction in the dark, addition of radical inhibitors).[18] Polymerization was not detected in our DMSO-mediated process.

Dehydrohalogenations are often accomplished in the presence of base, which removes the acidic proton α to the carbonyl to form a carbon anion followed by *β*-dehalogenation. Since there is no base used in the DMSO-mediated dehydrohalogenations, the reaction may occur via a keto−

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enol tautomerization process, during which the β-halogen atom is eliminated while the enol tautomerizes back to the keto form. The unique solvent properties of DMSO[19] favor the tautomerization process.

In the presence of base, the α-haloacrylate products with *E*-configuration have been obtained from dehydrohalogenation, which are the result of kinetic conditions.[20] Under the base-free conditions in DMSO, the *Z* double bond configuration of the olefin products from the reaction appears to be a reflection of the thermodynamic process. To confirm the thermodynamic feature of the DMSO-mediated dehydrohalogenation, we monitored the formation of 2-bromobut-2-enenitrile (entry 3 of Table 3) in DMSO-d_6. The reaction was complete within 1 h with a *Z*/*E* ratio of 1.00/0.77 in favor of the *Z* isomer (Figure 1). The population of the *Z* isomer increases to 1.00/0.60 with continuous heating at the same temperature for 8 h. Further heating for 24 h at the same temperature afforded a stable *Z*/*E* ratio of 1.00/0.47 (Figure 1).

In summary, a general and practical procedure for the conversion of activated α,β-dihalo compounds to the corresponding α-halo acrylate derivatives has been developed, and a variety of these α-halo Michael acceptors were prepared conveniently under mild and nearly neutral conditions. The DMSO used in the reaction serves as a reagent, as well as a solvent. Although dehydrohalogenation of α,β-dihalo compounds with other agents has been reported, the DMSO procedure is the most facile and environmentally benign process for such a transformation.

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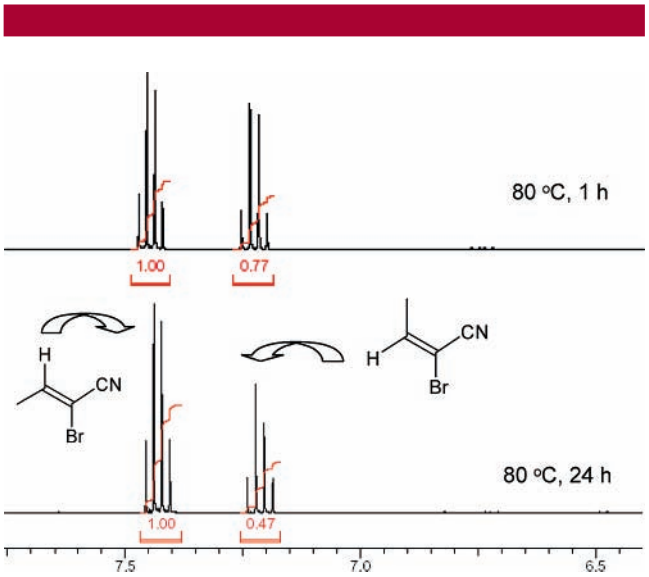

Figure 1. *E*/*Z* isomerization of 2-bromobut-2-enenitrile.

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Supporting Information Available: Typical experimental procedures for the preparation of α-haloacrylates with supporting analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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