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(*Z*)-1-Aryl-1-haloalkenes as Intermediates in the Vilsmeier Haloformylation of Aryl Ketones

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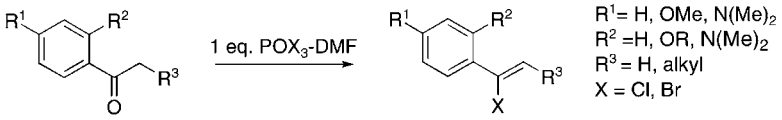
ABSTRACT



9a-i **10a-i**

Vilsmeier reagents give (*Z*)-1-aryl-1-haloalkenes from aryl ketones bearing an electron-donating substituent at the ortho- or para-position. These haloalkenes are intermediates in the Vilsmeier haloformylation of the aryl ketones. Another reaction mechanistic pathway is thus available in certain Vilsmeier haloformylations, in competition with the commonly accepted route by way of an enaminoketone.

Vilsmeier reagents are halomethyliminium salts best known for their use in the Vilsmeier−Haack formylation of activated aromatic rings.[1] The treatment of ketones with Vilsmeier reagent leads generally to the formation of *β*-halovinylaldehydes in a reaction often referred to as the Vilsmeier haloformylation.[2] It is generally accepted that the enolized ketone **2** is alkylated by the Vilsmeier reagent to form a *β*-*N*,*N*-dimethylaminovinyl ketone **3** that reacts further with the Vilsmeier reagent to give a bisiminiumchloride **4** (Scheme 1). The labile **4** is transformed into an iminium intermediate **5** and hydrolyzed into the *β*-chlorovinylaldehyde **6**. The formation of chloroalkene **8** byproducts or main products in Vilsmeier chloroformylation has been reported occasionally.[3] It is assumed that these chloroalkenes do not act as intermediates but arise from a nucleophilic substitution by chloride to a vinyl ether carbon of an iminium species **7** formed in electrophilic attack of the Vilsmeier reagent to the carbonyl group of the starting ketone **1**.[4] The formation of iminium species **7** liberates HCl, catalyzing the enolization required.

We now report that Vilsmeier reagents furnish (*Z*)-1-aryl-1-haloalkenes **10a**−**i** (Table 1, Scheme 2) from the corresponding ketones **9a**−**i**.[5] The reaction requires an electron-

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(4) However, Comins et al. have recognized that 4-chloro-1,2-dihydropyridines, which are cyclic chloroalkenes, were intermediates in the chloroformylation reaction of 2,3-dihydro-4-pyridones. See: (a) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *Tetrahedron Lett.* **1992**, *33*, 7635−7638. (b) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732−7739.

(5) **General Procedure for Synthesis of (*Z*)-1-Aryl-1-haloalkenes.** To a solution of DMF (1.2 mmol) in 0.5 mL of CH_2Cl_2 under argon at 0 °C was added POX_3 (1 mmol) dropwise. After 30 min, the ketone (1 mmol), dissolved in 1 mL of CH_2Cl_2, was added dropwise to the Vilsmeier reagent. The reaction mixture was allowed to reach room temperature and stirred as long as no starting material was detected on TLC. The reaction was quenched with saturated NaOAc and extracted with CH_2Cl_2. The organic layer was washed with brine and water and dried with Na_2SO_4; after filtration, the solvent was evaporated.

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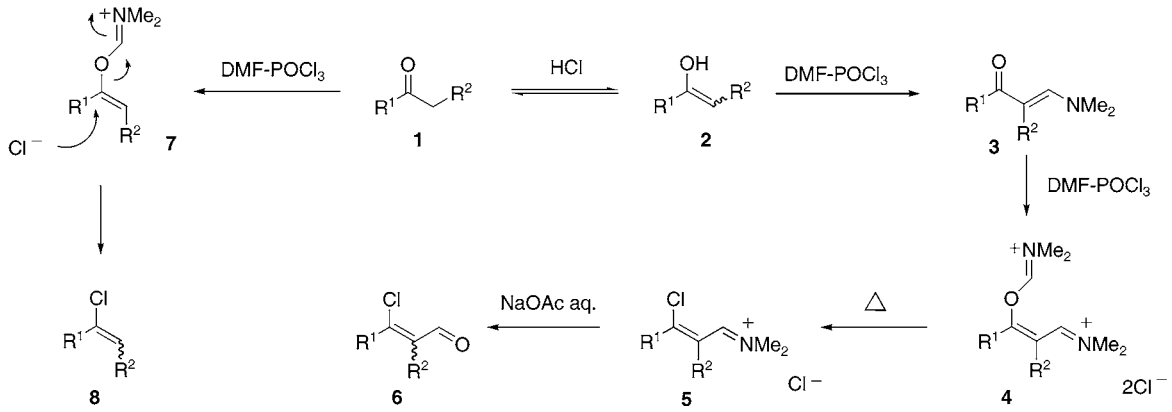
Scheme 1



donating group at the ortho- or para-position to the carbonyl group in the aromatic ring. It is interesting that the formation β-halovinylaldehydes from aryl ketones by Vilsmeier reagent has been reported frequently, but no haloalkenes were observed.[6]

Table 1. (*Z*)-1-Aryl-1-Haloalkenes Formed

10	R^1	R^2	R^3	X	yield[a] (%)	**11**[b] (%)
a	OMe	OMe	H	Cl	100	17
b	OMe	OMe	H	Br	93	6
c	OMe	OMe	CH_3	Cl	100	10
d	OMe	OMe	CH_3	Br	100[c]	2
e	$N(CH_3)_2$	H	CH_3	Cl	78	
f	$N(CH_3)_2$	H	CH_3	Br	96[c]	
g	$N(CH_3)_2$	H	H	Cl	91	13
h	H	$N(CH_3)_2$	H	Cl	95[d]	
i	OMe	$-(CH_2)_2-$		Cl	78[c]	2

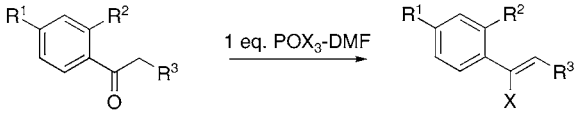
[a] Crude product. [b] Amount of the haloformylation product **11** in a crude product ^{1}H NMR spectrum. [c] With **10d** and **10f**, 9 and 5% of the (*E*)-isomer were formed, respectively. **10i** is an (*E*)-alkene. [d] After overnight stirring, 40% of the starting material was recovered.

The stereochemistry of the double bond formed was exclusively (*Z*)- for the chloro compounds. The stereochemistry was established by NOESY and one-dimensional ROESY NMR experiments. A clear correlation was found between the vinylic proton and the ortho proton in the aromatic ring. Small amounts of (*E*)-isomer were detected in the ^{1}H NMR spectrum when $POBr_3$ was used. With compound **10d**, 9% of the (*E*)-isomer was detected in the ^{1}H NMR spectrum,[7] and with **10f**, 5% of the (*E*)-isomer was detected. Bromoalkenes **10b**, **10d**, and **10f** readily form the acetylenic compounds by cleavage of HBr.[3a] When the formation of the (*Z*)-isomer was blocked as in the case of 6-methoxytetralone **10i**, the (*E*)-isomer was obtained instead.

Requisite reaction times and temperatures depend on the electron-donating ability of the substituents. *p*-(Dimethyl)-aminoacetophenone **9g** reacted at 0 °C in 2 min but methoxy-substituted aromatic ketones needed stirring at room temperature. At elevated temperatures, direct haloformylation and formylation of the aromatic ring become competing reactions. Meta-substituted and unsubstituted aryl ketones failed to give haloalkenes, as did halo- or alkyl-substituted aryl ketones. Corresponding β-halovinylaldehydes and recovered starting material were obtained instead. *p*-Methoxyacetophenone gave the corresponding β-chlorovinylaldehyde as a main product and only 25% of the expected chloroalkene.

Use of excess Vilsmeier reagent with aryl ketones **9a**−**i** leads to β-halovinylaldehydes, although 1-aryl-1-haloalkene intermediates can be detected when the reaction is monitored on TLC or by ^{1}H NMR. Similarly, when (*Z*)-1-aryl-1-haloalkenes **10a**−**i** are treated with the Vilsmeier reagent, β-halovinylaldehydes are obtained. For example, when **10e** was reacted with 2 equiv of $POCl_3$−DMF, 3-chloro-3-(4-dimethylaminophenyl)-2-methylpropenal **11e** was obtained in 61% yield and in an *E*/*Z* ratio[6f] of 1:6 (see Supporting Information). Vilsmeier reagents are known to formylate activated double bonds.[2e,c] This is clear evidence that haloalkenes are primary intermediates in the haloformylation reaction of suitably substituted aryl ketones.

Scheme 2



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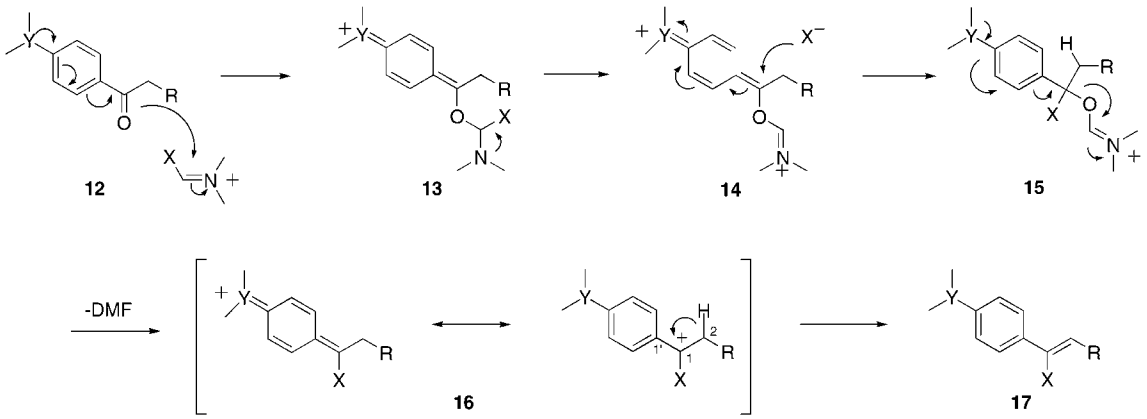
(7) (*E*)-1-Bromo-1-(2,4-dimethoxyphenyl)propene: ^{1}H NMR ($CDCl_3$) δ 1.50 (3H, d, J = 6.96 Hz), 3.82 (3H, s), 3.85 (3H, s), 6.26 (1H, q, J = 6.96 Hz), 6.45 (2H, m), 7.18 (1H, m).

Scheme 3



As regards the reaction mechanism, we suggest an electrophilic attack by the Vilsmeier reagent to the carbonyl group of the aryl ketone **12**, followed by loss of the halide, leading to the formation of a conjugated intermediate **14** (Scheme 3). In the following step, nucleophilic addition by the halide to the vinyl ether carbon restores aromaticity. Cleavage of DMF from **15** in an E1-type process generates the resonance-stabilized carbocation **16**, which subsequently loses a proton to give the final product **17**.

To explain the high stereoselectivity of the reaction, quantum-chemical density-functional calculations were performed, using the Turbomole program package and its standard basis sets.[8] The energy differences between the (*Z*)- (cis) and (*E*)- (trans) isomers of products **10c**−**f** were calculated using the B3LYP[9] hybrid functional in conjunction with a triple-ζ quality basis-set with polarization functions on all atoms, TZVP. The effect of the solvent CH_2Cl_2 was treated with the COSMO solvation model.[10] The relative energies between the isomers correlate reasonably well with the selectivity of (*Z*)-isomer; the smaller the energy difference in favor of the (*Z*)-isomer, the less selective the reaction becomes. For the chlorinated species **10c** and **10e**, the energy differences between the isomers were found to be −4.4 and −1.5 kcal/mol, respectively, and for the brominated species, **10d** and **10f**, +0.2 and −1.1 kcal/mol, respectively. At the current computational level, the (*E*)-isomer corresponding to **10d** is actually energetically favored.

The energy differences are, however, not large enough to be the sole explanation for the selectivity. Therefore, to further elucidate the mechanism involved, a more rigorous study of the final, reversible, deprotonation step in Scheme 3 was carried out. A potential energy surface (PES) for species **10e** was constructed (Figure 1), scanning the torsion angle C1′−C1−C2−C3, and the bond length of the leaving proton. The structures were relaxed and the energies evaluated using the computationally less demanding RI−BP functional[9b,10a,11] and the split valence SVP basis set. From the start, the (*Z*)-isomer is favored, the fully relaxed geometry of intermediate **16** having a torsion angle of 109° (B3LYP/

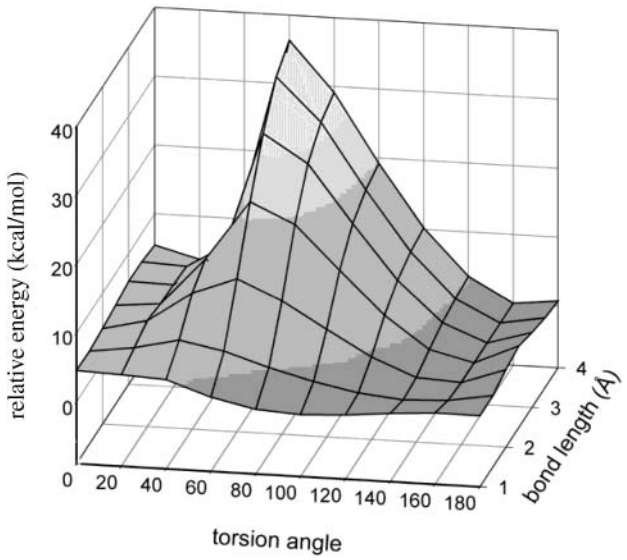


Figure 1. Potential energy surface for the deprotonation step (**16** and **17** in Scheme 3) for species **10e**. Energies relative to the lowest energy conformation for each proton bond length are shown. For the C1′−C1−C2−C3 torsion angle, 0° corresponds to the (*E*)-isomer and 180° to the (*Z*)-isomer.

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TZVP, species **10e**). The detachment of the proton quickly makes this favoritism more pronounced. At the same time as the equilibrium torsion angle shifts even more toward the (*Z*)-isomer, the transition to the (*E*)-isomer becomes more and more difficult as the double-bond character between C1 and C2 increases. A clear pathway toward pure (*Z*)-isomer can be discerned.

1-Aryl-1-haloalkenes are useful intermediates in organic synthesis. They have traditionally been synthesized by reacting ketones with PCl_5, but yields are often low and complex mixtures may be formed.[12] Phosphorus trihalides have also been used.[13] Haloalkenes have also been prepared by addition to alkynes producing mostly (*E*)-alkenes as syn adducts.[14] 1-Substituted (*Z*)-1-chloro-1-alkenes can also be produced by palladium-catalyzed Grignard coupling.[15] Recently, aryl-substituted (*Z*)-haloalkenes have been synthesized from aryl ketones using acetyl halides in strongly acidic solvent or with silica gel-supported zinc halides.[16] The assignment of stereochemistry as (*Z*)- on the basis of ^{1}H NMR shift values[17] agrees with our NOESY and ROESY NMR results (see Supporting Information).

In conclusion, the formation of (*Z*)-1-aryl-1-haloalkenes by Vilsmeier reagent is highly stereoselective. It is also shown, unlike previously thought, that the Vilsmeier haloformylation reaction probably proceeds via a haloalkene intermediate when suitable conjugation to an electron-donating group is present. Another reaction mechanistic pathway is thus available in certain Vilsmeier haloformylations, in competition with the commonly accepted route by way of an enaminoketone. A mechanism such as that postulated in Scheme 3 can undoubtedly apply for the previously reported[3] anomalous chloroalkene formations under Vilsmeier haloformylation conditions.[18]

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Supporting Information Available: ^{1}H and ^{13}C NMR and HRMS data of new compounds **10a**−**f** and **10h** and synthesis and characterization of compound **11e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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