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VILSMEIER REAGENTS: PREPARATION OF β-HALO-α,β-UNSATURATED KETONES

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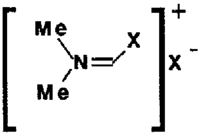
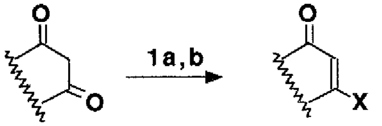
Abstract. *A new method for the preparation of β-chloro and β-bromo-α,β-unsaturated ketones from β-diketones is described. Utilizing Vilsmeier reagents (prepared from N, N-dimethylformamide and oxalyl chloride or oxalyl bromide) β-halo-α,β-unsaturated ketones are isolated in excellent yields.*

Vilsmeier reagents have been traditionally utilized as formylating reagents.[1] In recent years their versatility has also been demonstrated as activating agents for halogenation .[2] β-Diketones have been exposed to Vilsmeier conditions in the past, resulting in products derived from both formylation and halogenation .[3] In this report are described conditions which enable Vilsmeier reagents **1a,b**, to afford exclusively **halogenated** products from β-diketones (eq. 1). The corresponding β-halo-α,β-unsaturated ketones were isolated in yields ranging from 88-99% (Table 1).[4]



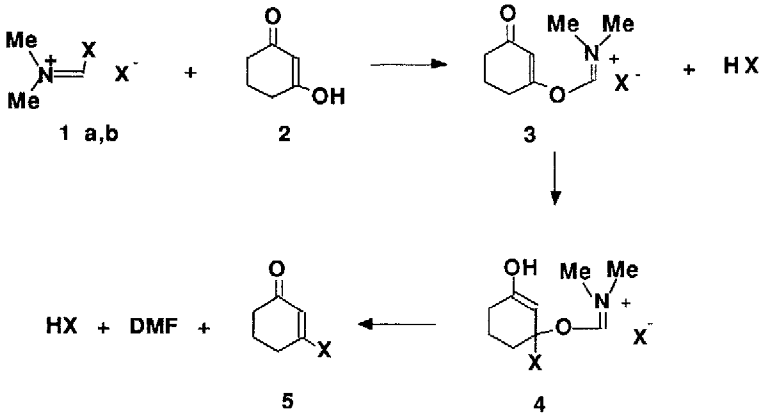
1a X=Cl
b X=Br



(1)

In preliminary studies, the Vilsmeier reagents were **preformed** [$(COX)_2$, DMF, CH_2Cl_2, 0 °C, 1 h], followed by the addition of the diketone. After further investigation, it was found to be more expedient to generate **1a,b** in the presence of the diketone.[5] This procedure allowed the entire reaction process to proceed in approximately 30 min. The reaction mechanism may be rationalized by the nucleophilic attack of diketone **2** with **1a,b,** forming **3** (Scheme 1). Conjugate addition of HX produces intermediate **4,** which undergoes decomposition to enone **5,** DMF, and HX.

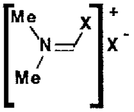
SCHEME 1

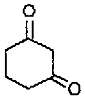
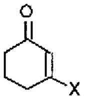
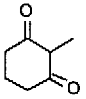
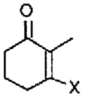
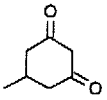
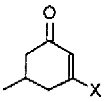
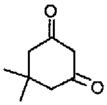
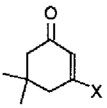
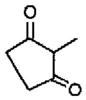
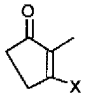
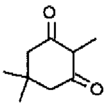
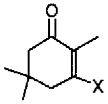


Interestingly, although **1a,b** can in principle be catalytic in the presence of $(COX)_2$, lower yields and much longer reaction times were observed when only 0.1 equiv. of DMF was employed. This may be explained by the existence of two competitive reaction pathways, both of which give the β-halo-α,β-unsaturated ketones. Clark and Heathcock reported that $(COCl)_2$ reacts with diketones generating β-chloro-α,β-unsaturated ketones.[4c] This process, which has also been confirmed in our labs, proceeds more slowly and requires higher reaction temperatures than the reaction pathway depicted in Scheme 1.[6] Therefore, apparently the β-diketones compete very effectively for the $(COX)_2$ when only catalytic amounts of DMF are present. Support for the presence of these parallel pathways is evident by the detection of small amounts of diene by-products, which Clark and Heathcock also observed.[4c] However, no by-products were detected when using greater than 1 equiv. of DMF.

Procedure. A mixture of the diketone (9 mmol), DMF (11.7 mmol, 1.3 equiv.), and CH_2Cl_2 (25 mL) was cooled to 0 °C and $(COX)_2$ (10.8 mmol, 1.2 equiv.) was added over 5 min with concurrent gas evolution. The reaction was allowed to warm to ambient temperature while stirring for approximately 30 min, and then poured into ether (100 mL) and water (40 mL). The organic layer was separated, dried over anhydrous magnesium sulfate and filtered. After removal of the solvent, the crude product was chromatographed through a short column of silica gel (25% EtOAc-hexanes). The solvent was removed using a rotary evaporator to afford the corresponding β-halo-α,β-unsaturated ketones (Table 1).

Further synthetic applications of **1a,b** as a halogenating agent are currently under investigation in our laboratories.

TABLE 1. Reaction of Diketones with 

Diketone	Reagent (X)	Product[7]	% Yield[a] ( )[b]
	Cl Br		93 (92) 89
	Cl Br		91 95 (90)
	Cl Br		95 98
	Cl Br		96 99 (93)
	Cl Br		94 88 (82)
	Cl Br		94 92

a. Yield of isolated product (silica gel chromatography).

b. Yield of isolated product using **preformed 1a,b**.

References and Notes

1. a) A. Vilsmeier and A. Haack, *Chem Ber.* **1927**, 60, 119. b) C. Jutz in "Iminium Salts in Organic Chemistry," ed. H. Boehme and H. G. Viehe, Part 1, Vol. 9, 225, Wiley Inter-Science, New York (1976). c) Z. Arnold and A. Holy, *Collect. Czech. Chem. Commun.* **1961**, 26, 3059.

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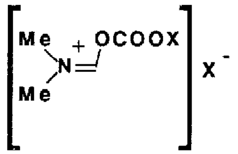
3. a) M. Pulst, B. Hollborn, and M. Weissenfels, *J. Prak. Chem.* **1979**, 4, 671. b) A. R. Katritzky and C. M. Marson, *Tetrahedron Lett.* **1985**, 4715.

4. For other methods see a) E. Piers, J. R. Grierson, C. K. Lau, and I. Nagakura, *Can J. Chem.* **1982**, 60, 210. and references therein. b) L. Gruber, I. Tomoskozi, and L. Radics, *Synthesis* **1975**, 708. c) R. D. Clark and C. H. Heathcock, *J. Org Chem.* **1976**, 41, 636 and references therein.

5. This method reduces the overall reaction time and avoids any solubility problems associated with the diketones and Vilsmeier reagents. The possibility that **1a,b** may have



the following structure, should not be ruled out . However, it should be noted that both methods afford the corresponding β-halo-α,β-unsaturated ketones in similar yields (see Table 1).

6. This observation suggests that the formation of the intermediate β-diketo-oxalate esters competes effectively with the catalytic Vilsmeier reagent cycle. However, when at least 1 equiv. of DMF is present, the DMF reacts much faster than the diketone with $(COX)_2$.

7. Satisfactory analytical data were obtained for all compounds.

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