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Correspondence

Potential Toxicological Concerns Associated with Carboxylic Acid Chlorination and Other Reactions†

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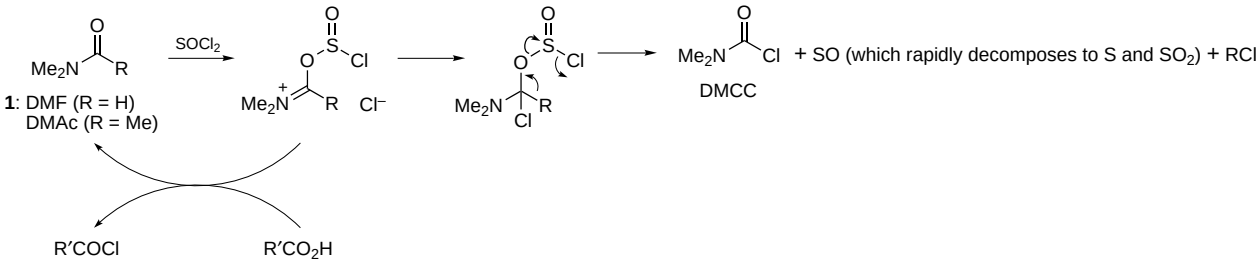
Scheme 1



Use of dimethylformamide (DMF) as a catalyst to accelerate chlorodehydroxylations (for example, in preparation of acyl halides by reaction of the corresponding carboxylic acids with thionyl chloride) is a well-established procedure.[1] During our recent evaluation of this chemistry, however, we identified dimethylcarbamoyl chloride (DMCC) as a minor reaction by-product formed at levels of up to a few thousand parts per million (corresponding to conversion of a substantial proportion of the DMF used as chlorination catalyst). Whilst this by-product formation is of limited concern with respect to the required reaction yield, it is of potentially significant concern in the context of DMCC toxicology in that DMCC is a known animal carcinogen[2] and a potential human carcinogen[3] necessitating control of exposure to very stringent standards, measured in terms of only a few parts per billion.

Whilst reaction of DMF with chlorinating agents to give DMCC is known,[4] the lack of obvious references to the potential toxicological concerns associated with use of DMF as a catalyst for chlorination reactions suggests that the potential for generation of DMCC as a toxic by-product from such reactions may not be generally appreciated.

A suggested mechanism for formation of DMCC from reaction of thionyl chloride and DMF (**1**, R = H) is outlined in Scheme 1, from which it is clear (by analogy) that DMCC could also be generated under alternative chlorination conditions [*e.g.*, with use of *N*,*N*-dimethylacetamide as catalyst (**1**, R = Me) in place of DMF, or with use of other chlorinating agents such as phosgene or phosphorus oxychloride in place of thionyl chloride]. It is accordingly recommended that the presence of DMCC should be assessed (down to parts per billion levels) and appropriate measures for containment be taken whenever DMCC generating conditions (including other reactions involving chlorinating agents and DMF or other amides, *e.g.*, Vilsmeier−Haack formylation[5]) are employed.

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(1) *E.g.*: Buehler, C. A.; Pearson, D. E. *Survey of Organic Syntheses*; Wiley-Interscience: New York, 1970; p 861. Sumitomo Seika Chem Co Ltd. Patent JP 6063407, 1994. Berlin Chemie VEB. Patent DD 220597, 1987. Chevron Research Co. Patent US 4129595, 1978. Foken, H. Patent DD 121928, 1976. Pennwalt Corp. Patent US 3557205.

(2) EC Cat. 2 animal carcinogen reference Annex 1 Dangerous Substances Directive 67/548/EC.

(3) *IARC Monogr. Eval. Carcinog. Risk Humans* **1974**, *12*, 77.

(4) *E.g.*: Lvov Polytechnic. Patent SU 267629. Schindler, N.; Ploger, W. *Chem. Ber.* **1971**, *104*, 969. Hasserodt, U. *Chem. Ber.* **1968**, *101*, 113.

(5) *E.g.*: Jackson, W. G.; *et al. J. Am. Chem. Soc.* **1981**, *103*, 533.

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