Synthesis of Acyl Halides under very Mild Conditions

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Summary On treatment with tetramethyl-α-halogenoenamines at room temperature or below, carboxylic acids are converted into acyl halides in high yields under neutral conditions.

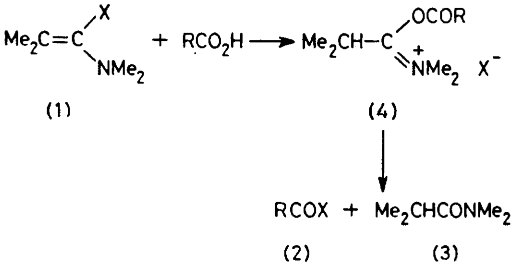
WE report here the preparation of several acyl halides from carboxylic acids at room temperature or below† under essentially neutral conditions using the tetramethyl-α-halogenoenamines (**1**). Large quantities of (**1a**) may be readily prepared,[1] the tetramethyl-α-fluoro- and α-iodo-enamines (**1b**) and (**1c**) may be formed from (**1a**) with KF and KI, respectively,[2] and the tetramethyl-α-bromoenamine (**1d**) is most readily obtained by refluxing (**1a**) for 24 h in a seven-fold excess of dibromomethane (yield 78%, b.p. 150—152 °C).

TABLE. Preparation of the acyl halides (**2**) RCOX[a]

R	X	Yield/%[b]	R	X	Yield/%[b]
Cl_3C	Cl	100	Cl_3C	F	100
Bu^t	Cl	100, 70[c]	Bu^t	F	100
CH_2=CH–	Cl	96	Ph	F	100
1,3-Dithiolan-2-yl	Cl	100	Cl_2CH	F	98
N_2CH[d]	Cl	100	MeCH=C(Me)	F	97
$(MeO)_2CH$[e]	Cl	94	H[l]	F	100
HCO[f]	Cl	96[g]	Bu^t	Br	100
MeCO[h]	Cl	100[g]	CH_2=CH[2]	Br	100
PhCO[i]	Cl	80[j]	H[i]	Br	100
$CH_2(COCl)_2$		100	Me	I	100
Pyrrol-2-yl	Cl	100	Ph	I	100
Furan-2-yl	Cl	100	Bu^t	I	100
H[k]	Cl	94[g]	H[f]	I	100

[a] Reactions were carried out at 20 °C unless otherwise stated. [b] Determined by n.m.r. spectroscopy using an added standard. [c] Isolated from (**6**). [d] −10 °C, 3 h. [e] −40 °C, 1 h. [f] −20 °C. [g] Yield of isolated methyl ester. [h] −20 °C, 4 h. [i] 0 °C. [j] Yield of isolated anilide. [k] −60 °C, 1 h. [l] −30 °C, 1 h.

Dichloromethane solutions of carboxylic acids were treated with equimolar amounts of (**1**) (Table). At room temperature, the acids were instantaneously transformed into the acyl halides (**2**) and *NN*-dimethylisobutyramide (**3**) with no formation of the hydrogen halide. For the thermally unstable acyl halides, lower temperatures and longer reaction times were used. Excellent yields were obtained even for unstable acyl halides. Acyl iodides can also be readily prepared by this method.

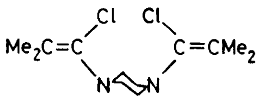


a; X = Cl
b; X = F
c; X = I
d; X = Br

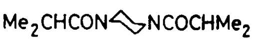
The reaction involves the rapid formation of (**4**) which could be detected by n.m.r. spectroscopy (*e.g.* at −30 °C when R = H, X = Cl). Addition of halide ion to the carbonyl group of (**4**) followed by elimination of the amide (**3**) accounts for the formation of (**2**).

Since the only by-product is the relatively inert amide (**3**), isolation of the acyl halides for further reaction will often be unnecessary. When the purification of an acid chloride is necessary and cannot be effected by fractional distillation, the alternative reagent (**5**) can be used. It was prepared by treating *NN'*-di-isobutyrylpiperazine (**6**) for 3 days with an excess of phosgene in CH_2Cl_2 containing a catalytic amount of dimethylformamide (DMF). Removal of the volatile material left a residue which, on heating *in vacuo* for 3 h at 150—170 °C, gave (**5**) (60% yield), m.p. 137 °C. Reaction of (**5**) at 20 °C for 2 h with 2 mol. equiv. of the carboxylic acids in CH_2Cl_2 also yielded the corresponding acid chlorides. Evaporation of the solvent and addition of hexane (or low-boiling light petroleum) to the residue caused the crystallisation of most of the bisamide (**6**).

The reagents (**1a**), (**1c**), (**1d**), and (**5**) can be used equally



(**5**)



(**6**)

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† *NN*-Dimethyl-1,2,2-trichlorovinylamine has been reported (A. J. Speziale and R. A. Freeman, *J. Amer. Chem. Soc.*, 1960, **82**, 909) to convert acetic and benzoic acids at 50—85 °C into the corresponding acyl chlorides (75 and 66%).

successfully to convert alcohols into the corresponding halides. These results will form the subject of a separate paper.

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