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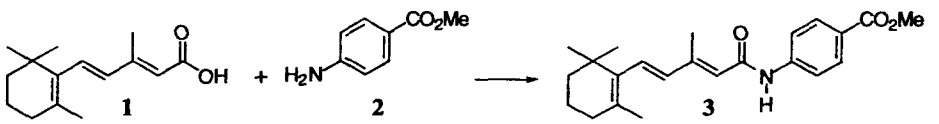
A RAPID, MILD AND ACID-FREE PROCEDURE FOR THE PREPARATION OF ACYL CHLORIDES INCLUDING FORMYL CHLORIDE

G. B. Villeneuve*, and T. H. Chan

Department of Chemistry, McGill University, Montréal, Québec H3A 2K6, CANADA

Abstract: Carboxylic acids are converted by hexachloroacetone and triphenylphosphine at -78 °C in methylene chloride to the corresponding acyl chlorides. Formic acid can be used to generate formyl chloride at -78 °C in order to perform formylation under very mild conditions.

Despite the fact that many coupling agents have been developed for the formation of amide bonds directly from acids and amines, there is still a need to rely on the use of acyl chlorides for amide synthesis. A case in point is our recent experience in trying to form the amide **3** from the carboxylic acid **1** and the amine **2**. Coupling agents such as dicyclohexylcarbodiimide (DCC)[1], diphenylphosphoryl azide (DPPA)[2], 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)[3], and bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl)[4] had all proved to be inefficient. In this case the poor reactivity of the deactivated aromatic amine in concomittance with the conjugated nature of the activated carboxylic acid derivative may explain the failure of the coupling reaction. Moreover, despite the fact that the acyl fluoride corresponding to **1** can be prepared in high yield by the procedure of Olah et al,[5] no clean coupling with **2** could be obtained after several days in pyridine at room temperature. When the acyl chloride corresponding to **1** was prepared with oxalyl chloride and a catalytic amount of dimethylformamide, the desired amide **3** could be obtained in 15% yield. This poor yield might be ascribed to the sensitivity of **1** (or its acyl chloride derivative) to hydrochloric acid generated *in situ* by the reactants. We were thus searching for a mild method for the conversion of **1** to its acid chloride under acid free condition.



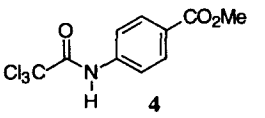
1 **2** **3**

Lee had previously described the use of triphenylphosphine (TPP) and carbon tetrachloride for the convertion of carboxylic acids to acyl chlorides,[6] analogus to the conversion of alkyl alcohols to alkyl chlorides.[7] This method required however temperatures above room temperature and concentrated reaction mixture in order to proceed. Cyanuric chloride had also been used to carry out such a transformation but with relatively longer reaction time at room temperature.[8] Finally, tetramethyl-α-chloroenamine can be used for forming acyl chlorides at temperatures as low as -60 °C;[9] however the preparation of tetramethyl-α-chloroenamine required the use of phosgene.[10]

It has been demonstrated that hexachloroacetone (HCA) can substitute for carbon tetrachloride in the conversion of alcohols to chlorides and moreover allow the reaction to take place at 10 °C.[11] Under such reaction conditions, allylic alcohols are converted to allylic chlorides without allylic rearrangement. To our knowledge, the application of this procedure of using HCA/TPP for the conversion of carboxylic acids to acyl chlorides has not been reported in the literature and is the subject of our investigation.

As a first attempt, we used reaction conditions similar to those described by Maglid et al.[11] which consisted of dissolving **1** in HCA as a reaction solvent at 10 °C and then adding the finely grounded triphenylphosphine. The conversion of **1** to the acyl chloride presumably occurred in view of the disappearance of the solid triphenylphosphine (which was otherwise not soluble in HCA).[12] The putative formed acyl chloride was then added dropwise to a solution of **2** in pyridine at 0 °C which led to a 40% yield of the desired amide **3** after purification by silica gel column chromatography. Analysis of the main side product led to the identification of trichloroacetamide **4**. This formation of **4** was not unexpected since Panetta and Casanova[13] had already reported trichloroacetylation of amines in dimethylsulfoxide in the presence of HCA. The side product **4** was then clearly due to the presence of a large excess of HCA under the Maglid conditions.

In order to optimise the reaction conditions to reduce trichloracetamide formation, we used benzoic acid and benzylamine as the model reaction. We found that only 1 mmol of HCA with 1 mmol of triphenylphosphine in dichloromethane were required to convert benzoic acid to benzoyl chloride quantitatively.[14] Furthermore, we observed that the reaction temperature could be lowered to -78 °C without significant difference in conversion time.[15] However, despite the total transformation of benzoic acid to benzoyl chloride as monitored by TLC, amide formation with benzylamine remained less than quantitative as one would have expected (which was the case by combining directly benzoyl chloride with benzylamine in stoichiometric amounts). The reaction gave rise to two side products **6** and **7** in addition to the desired N-benzylbenzamide (**5**). The yield of **5** depended on reaction conditions and are summarized in Table 1. At most, 73 % of the desired material **5** was obtained. The two side products were the expected N-benzyl-trichoroacetamide (**6**) as well as a substantial amount of N-benzyl-dichloroacetamide (**7**). We attributed the formation of **7** to the pentachloracetone counteranion of the triarylphosphonium chloride species (**8**) which could react with a free amine to form the dichloroacetamide with the generation of the trichloromethyl carbanion. A possible solution to suppress the formation of both **6** and **7** was to use even less HCA relative to triphenylphosphine. The assumption was that the complex·**9** could well be formed under such conditions, and the dianion species would not be an effective acylating agent. Indeed when the ratio of HCA/TPP was reduced to 1/2, benzoic acid was still converted to benzoyl chloride in a quantitative manner, and on reaction with benzylamine, the sole product obtained was N-benzylbenzamide in very high yield either at -78 °C or at room temperature (Table 1). It was gratifying to find that when the coupling of **1** and **2** was conducted under the same conditions, an essentially quantitaive yield of **3** was obtained. It is worth noting that owing to the poor solubility of **1** in cold dichloromethane, the reaction was conducted in anhydrous tetrahydrofuran without affecting the yield.



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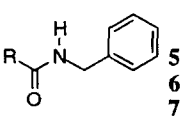
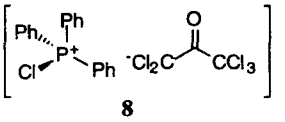


5 R = Ph
6 R = CCl_3
7 R = $CHCl_2$



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With an efficient and mild method for the conversion of acids to acid chlorides in hand, we became interested to see if the method could be applied to the generation of the highly reactive formyl chloride. Formyl chloride had been generated for the first time by Staab and Datta[16] and later by Devos et al.[9] It was found to be stable only at temperature below -60°. When formic acid (commercial, 100%) was treated with 2 moles of TPP and 1 mole of HCA in dichloromethane at -78°, and then followed by quenching with *p*-methylaniline, a 88 % yield of formylation was obtained for the formation of N-4-methylphenyl-formamide. In this reaction, a 2 fold

excess of formic acid was used relative to the amine in order to compensate for the fact that commercial 100 % formic acid may not be completely anhydrous (Table 1).

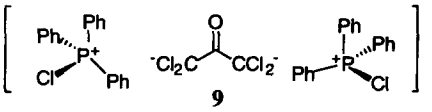

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Table 1. Formation of Acyl Chlorides and Reaction with Amines under Various Conditions

RCO_2H	RNH_2	base[a]	solvent	Reagents ratio[b]	Method[c]	Temperatures[d]	Yield[e](%)
1	**2**	Pyr.[f]	HCA	13:1:1:1:25	A	10, 10, 0	40
$PhCO_2H$	$PhCH_2NH_2$	Pyr.	CH_2Cl_2	1:1:1:1:12	C	-78, -78, -78	60
$PhCO_2H$	$PhCH_2NH_2$	NEt_3	CH_2Cl_2	1:1:1:1:2	C	20, -78, -78	53
$PhCO_2H$	$PhCH_2NH_2$	Pyr.	Pyr.	1:1:1:1:36	B	-78, -78, -78	21
$PhCO_2H$	$PhCH_2NH_2$	Pyr.	CH_2Cl_2	1:1:1:1:12	B	-78, -78, -78	64
$PhCO_2H$	$PhCH_2NH_2$	Pyr.	CH_2Cl_2	1:1:1:1:12	B	20, 20,20	73
$PhCO_2H$	$PhCH_2NH_2$	NEt_3	CH_2Cl_2	1:2:2:2:2	B	20, 20, 0	100
$PhCO_2H$	$PhCH_2NH_2$	NEt_3	CH_2Cl_2	1:2:2:2:2	B	-78, -78, -78	95
HCO_2H	*p*$MePhNH_2$	NEt_3	CH_2Cl_2	1:2:2:2:2	B	-78, -40, -78	11
HCO_2H	*p*$MePhNH_2$	NEt_3	CH_2Cl_2	1:2:2:2:2	B	-78, -78, -78	30
HCO_2H	*p*$MePhNH_2$	NEt_3	CH_2Cl_2	1:2:2:1:2	B	-78, -78, -78	88
1	**2**	Pyr.	THF	1:2:2:2:12	B	-78, -78, -78	99

a) Pyr: Pyridine; b) Ratio in mmol of HCA:carboxylic acid:triphenylphosphine:amine:base; c) Method A: carboxylic acid was dissolved in HCA at temperature T_1, TPP finely powdered was then added at temperature T_2, this mixture was then added to the corresponding amine in pyridine at temperature T_3; method B: HCA and carboxylic acid in solvent at temperature T_1, TPP in solvent was added and temperature raised to T_2, amine in solvent is added at temperature T_3, base in solvent is added at temperature T_3; method C: TPP in solvent added to HCA in solvent at temperature T_1, carboxylic acid in solvent added at temperature T_2, amine in solvent added at temperature T_3, base in solvent is added at temperature T_3; d) T_1, T_2, T_3 (°C); e) isolated yield after column chromatography; f) pyridine was distilled over sodium.

EXPERIMENTAL

N-benzylbenzamide: A mixture of benzoic acid (122 mg, 1 mmol) and hexachloroacetone (132 mg, 0.5 mmol) in methylene chloride (2 ml) was stirred under argon and cooled down to -78 °C. Triphenylphosphine (262 mg, 1mmol) in methylene chloride (1 ml) was added dropwise and the mixture was stirred for 20 min. The acyl chloride solution was then treated with a solution of benzylamine (107 mg, 1 mmol) in methylene chloride (1ml) dropwise followed by triethylamine (101 mg, 1mmol) in methylene chloride (1 ml). The reaction mixture was then allowed to reach room temperature after which the solvent was evaporated under high vacuum. The dry residue was suspended in 20 % ethyl acetate in hexane (4 ml) and silica gel added in order to obtain a pasta. This pasta was added onto the top of a silica gel column and the elution performed with the same solvent. The pure fractions provided the title compound as a white solid (187 mg, 95%): m. p. 102 °C (corr.), litt 104-106 °C. Spectroscopic data were consistent with published data.

N-4-methylphenylformamide: The procedure was the same as mentioned above except that the reagents were formic acid 100 %[17] (92 mg, 2 mmol), hexachloroacetone (264 mg, 1mmol), triphenylphosphine (524 mg, 2 mmol), *p*-methylaniline (107 mg, 1 mmol), and triethylamine (202 mg, 2 mmol). After column chromatography, the title compound was obtained as a white solid (119 mg, 88 %). m.p. 53-54 °C (corr.) ^1H

NMR ($CDCl_3$) all signals were doubled owing to *cis-trans* (ration 1: 1.3) amide equilibrium 2.32 (s, 3H), 2.34 (s, 3H), 6.99 (m, 2H), 7.15 (m, 4H), 7.43 (m, 2H), 7.6 (br s, 1H, NH), 8.33 (d, J = 1.8 Hz, 1H, C*H*O amide *trans*), 8.5 (br s, 1H, NH), 8.64 (d, J = 11.4 Hz, 1 H, C*H*O amide *cis*); ^{13}C NMR ($CDCl_3$) 22.37, 22.45, 119.56, 120.48, 129.84, 130.50, 134.37, 134.57, 134.70, 135.35, 158.98, 162.76; ^{1}H NMR ($DMSOd_6$) signals were doubled owing to *cis-trans* (ratio 1:3) amide equilibrium 2.26 (s, 3H), 7.12 (m, 2H, Ar *trans* + m, 4H Ar *cis*), 7.48 (m, 2H, Ar *trans*), 8.25 (d, J = 1.9 Hz, 1H, C*H*O amide *trans*), 8.72 (d, J = 11.1 Hz, 1 H, C*H*O amide *cis*) 10.02 (br s, 1H, NH *cis*), 10.09 (br s, 1H, NH *trans*); ^{13}C NMR ($DMSOd_6$) 27.03 (*cis*), 27.17 (*trans*), 123.27 (*cis*), 124.66 (*trans*), 134.62 (*trans*), 135.19 (*cis*), 137.90 (*trans*), 138.09 (*cis*), 140.5 (*cis*), 141.11 (*trans*), 164.37 (*trans*), 167.46 (*cis*);

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14. Benzoyl chloride moved well without decomposing on TLC, and therefore its formation from benzoic acid was easily assessed. On the other hand, the acyl chloride of carboxylic acid **1** decomposed on TLC.
15. It has already been reported that anhydrides of carboxylic acids can be formed with a stoichiometric amount of hexamethylphosporane triamine and carbon tetrachloride at -78 °C. Casto, B.; Doromoy, J. R. *Bull. Soc. Chim. Fr.* **1971**, *8*, 3034-3036.
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17. Formic acid 98-100 % from American Chemicals Ltd. (Montréal) was used as supplied. The latter froze when kept at 5 °C for 24 h. Lower grade formic acid did not give rise to the desired reaction.

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