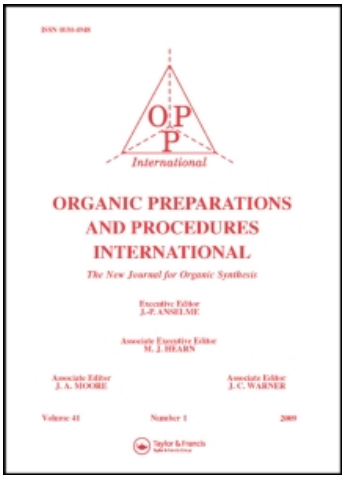

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IMPROVEMENT OF THE VILSMEIER-HAACK REACTION

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styrene, 1.02 min; 1-phenethyl formate, 3.87 min; 1-bromoethyl benzene, 4.83 min; 2-bromoethyl-benzene, 6.35 min; 1-methylnaphthalene, 9.19 min.

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† Dedicated to Professor E. V. Dehmlow on the occassion of his 60th birthday.

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IMPROVEMENT OF THE VILSMEIER-HAACK REACTION

Submitted by (10/15/92)

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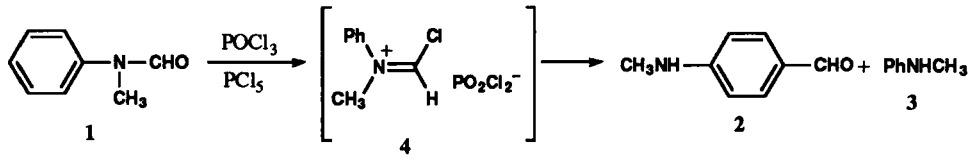
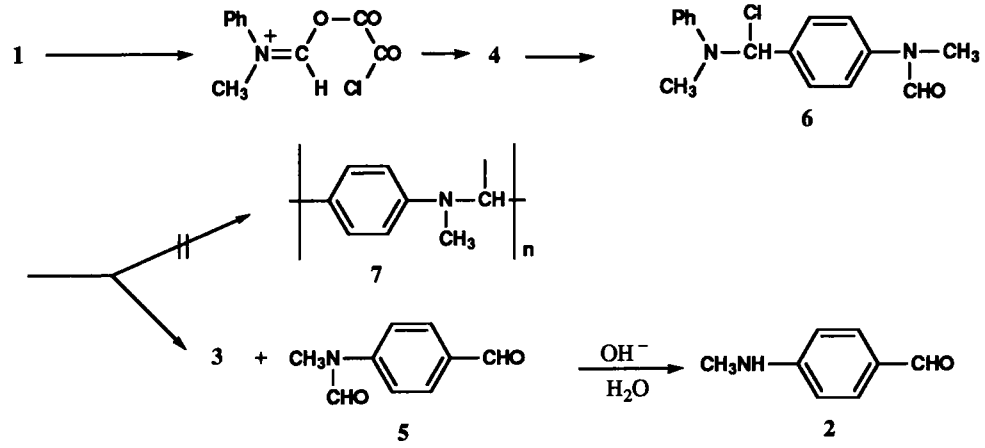
During the course of a study of the asymmetric alkylation and deracemization of α-amino acids supported on a chiral polymer,[1] we required compound **2** in order to prepare one of the monomeric precursors. It has been reported[2] that treatment of N-methylformanilide (**1**) with a mixture of $POCl_3$ and PCl_5, gives *p*-N-methylaminobenzaldehyde (**2**) in 33% yield. However, when the literature conditions were used, the yields were erratic ranging from 15-30%. Moreover, purification of the product is somewhat difficult on account of the numerous by-products. We therefore undertook a study of the experimental conditions of the Vilsmeier-Haack reaction,[3] such as dilution with a solvent, the use of various halogenated reagents, the relative quantities of reagents, the reverse addition of reagents, etc.



It was found that the use of a solvent (CH_2Cl_2, $CHCl_3$, AcOEt, etc.), gave less than 10% yield. We found it unnecessary to use a mixture of $POCl_3$ and PCl_5, since similar results were obtained with each of these reagents alone. On the other hand, with $SOCl_2$ the expected compound was not formed. The Vilsmeier salt **4** failed to react with N-methylaniline **3**; when **3** was added to the reagent mixture, no **2** could be isolated. The Vilsmeier complex [Cl-CH=N$^+$(CH$_3$)$_2$ Cl$^-$] of oxalyl chloride with dimethylformamide has been employed in numerous reactions such as esterification,[4] reduction,[5] halogenation,[6] formation of acyl chlorides,[7] etc. However, oxalyl chloride alone has not been used in the formylation of aromatic substrates.

Addition of an equimolecular quantity of oxalyl chloride without solvent to N-methylformanilide (**1**) gave *p*-formyl-N-methylformanilide (**5**) (26%), N-methylaniline (**3**) (26%) in addition to unreacted N-methylformanilide (48%). These results suggest the following mechanism.

The intermediate formation of *p*-formyl-N-methylformanilide (**5**), which can be easily isolated by chromatography on a silica gel column and the formation of equimolecular quantities of **3** and **5** suggest that **6** does not react with **1** and oxalyl chloride to give an oligomer such as **7**. Under these conditions and according to the mechanistic scheme below, the yield cannot exceed 50%. The low yield (26%) of *p*-formyl-N-methylformanilide is at least partially the result of a loss of oxalyl chloride, the latter being carried away in the vigorous gas evolution during the reaction. By using two equivalents of reagent, the yield of **2** increased to 40%. *p*-Methylaminobenzaldehyde (**2**) was obtained



nearly quantitative yield following by treatment of **5** with 6N NaOH. This basic hydrolysis could also be performed directly on the crude reaction mixture. In the latter case, N-methylaniline must be eliminated by steam distillation and **2** extracted with CH_2Cl_2. Few by-products are formed thus allowing

ready isolation of **1** in the pure state. The addition of solvent (CH_2Cl_2) at the end of the introduction of oxalyl chloride decreased the yield (6.5%). Finally, no **2** was obtained when the Vilsmeier complex was pre-generated by reaction of oxalyl choride with DMF, either with or without solvent.

In conclusion, the use of oxalyl chloride in the formylation of N-methylformanilide provides the following advantages: (a) improved yields approaching the theoretical maximum of 50 %, (b) good reproducibility, and (c) few by-products.

EXPERIMENTAL SECTION

Mps are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on a Brucker AC 250 instrument, using TMS as an internal standard.

***p*-(N-Methylamino)benzaldehyde (2).**- An equimolecular quantity of oxalyl chloride (19.4 mL, 0.22 mole) was added without solvent to N-methylformanilide (30g, 0.22 mole) at such a rate that the temperature was maintained between 40-50°. Stirring was then continued for 12 hrs at room temperature. The resulting viscous oil was dissolved in 150 mL of water and the solution made basic with a 6N sodium hydroxyde solution. The by-product N-methylaniline was removed by steam distillation and the residual solution was extracted with CH_2Cl_2 (3 x 30 mL). The combined CH_2Cl_2 extracts were dried over sodium sulfate and the solvent was removed *in vacuo*; the residual crystallized red oil was distilled to give 7.75 g (26%) of pure product, bp. 127-130°/0.04mm, lit. bp. 185-187°/15mm.[2] By using two equivalents of oxalyl chloride and with the same experimental procedure pure **2** was obtained in 40% yield after distillation. R_f = 0.60 (SiO_2, CH_2Cl_2-AcOEt 2:1); mp = 54°; ^1H-NMR ($CDCl_3$ / TMS): δ 2.80 (d, 3H); 6.72 (d, 2H); 7.75 (d, 2H); 10.10 (s, 1H).

***p*-Formyl N-methylformanilide (5)** may be isolated from the reaction mixture obtained above. After being stirred for 12 hrs at room temperature, the resulting viscous oil was hydrolysed with water and neutralized with a saturated sodium acetate solution (pH 5-6). After extraction with CH_2Cl_2, the organic phase was dried over sodium sulfate and the solvent was evaporated. The residual solid thus obtained was chromatographed on silica gel with 1:1 AcOEt-CH_2Cl_2 as eluent; R_f = 0.67. ^1H NMR ($CDCl_3$/TMS): δ = 3.45 (s, 3H); 6.78 (d, 2H); 8.13 (d, 2H); 8.90 (s, 1H); 10.20 (s, 1H).

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.14 ; H, 5.69; N, 8.71

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SYNTHESIS OF 2-HYDROXY-3-METHYLCYCLOPENT-2-EN-1-ONE FROM LINALYL ACETATE

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2-Hydroxy-3-methylcyclopent-2-en-1-one (**6**, corylone) is a commercially important perfumery and flavouring material. In 1963, it was identified, along with some other cyclic 1,2-diketones, as a component of the roasted coffee aroma complex.[1] Mainly because of its organoleptic properties **6** has been the target of a great deal of synthetic activity. Indeed, its value does not reside solely on its aroma and flavor: the compound has also been found useful as a synthetic precursor of cyclopentenoid natural products, including dihydrojasmone,[2] methylenomycin B[3] and oxaprostaglandins analogs.[4] A preceding paper, described a synthesis of 2-hydroxy-3-methylcyclopent-2-en-1-one (**6**). The key to this synthesis was the preparation of 2-hydroxy-2-methylglutaric acid dimethyl ester (**4**) from 2-ketoglutaric acid.[5] The present work, describes a alternative synthesis of compound **4** starting from linalyl acetate (**1**).

Treatment of linalyl acetate by von Rudloff permanganate-periodate method[6] gave 2-acetoxy-2-methylglutaric acid (**2**). Methylation of this crude product with diazomethane[7] gave 2-acetoxy-2-methylglutaric acid dimethyl ester (**3**). Our initial intent was cyclize diester **3** by the acyloin condensation to give the bis(trimethylsilyl) ether (**7**).[8] Simple hydrolysis and dehydration of this ether would give **6**. To our surprise, however, the reaction of **3**, under the usual conditions[9] used for the acyloin condensation failed. We suspected the source of our problem to be the presence of the group acetoxy. In order to overcome this problem, compoud **3** was treated with K_2CO_3/MeOH to give **4**. It was necessary to protect the hydroxyl group before acyloin condensation. The trimethylsilyl ether (**5**),