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# Oxidation of *N*-Acyl-Pyrrolidines to Imides with $CrO_3$·3,5-Dimethylpyrazole

Gonzalo Blay, Luz Cardona, Begoña García, Cristina L. García and José R. Pedro*

Departament de Química Orgànica, Facultat de Química, Universitat de València, 46100 Burjassot (València) Spain.

***Abstract***: *N*-Acyl-pyrrolidones are easily obtained by treatment of *N*-acyl-pyrrolidines with $CrO_3$·3,5-dimethylpyrazole complex ($CrO_3$·3,5-DMP) at room temperature. © 1997 Elsevier Science Ltd.

Imides are used as valuable intermediates in organic synthesis as well as in biologically active compounds like drugs, fungicides and herbicides. Their preparation is usually carried out by *N*-acylation of amides with a suitable acylating agent.[1] However oxidation of amides to imides has not been widely explored as amides show low reactivity toward oxidants, and only few methods have been reported in the literature: $RuO_4$ (in stoichiometric or catalytic amount),[2-6] iron(II)-$H_2O_2$ in aqueous acetonitrile[7] and the electrochemical anodic oxidation with *N*-hydroxyphthalimide as mediator[8] give good results with several *N*-acyl amines.

Chromium-based oxidants are probably the most widely used of all oxidizing agents and they have been continually developed and modified over the years. The $CrO_3$·3,5-dimethylpyrazole complex ($CrO_3$·3,5-DMP) is a good oxidant that gives excellent results in the oxidation of alcohols to aldehydes and ketones.[9] It has proved also to be a better reagent than other well known related oxidants such as Collins reagent and pyridinium chlorochromate (PCC) for allylic C-H bonds.[10] Surprisingly, the true scope of the oxidant ability of this complex has not been reported.

In this *Letter* we report that $CrO_3$.3,5-DMP brings about the oxidation of aliphatic and aromatic *N*-acyl-pyrrolidines to the corresponding *N*-acyl-pyrrolidones in good yields, which makes it a reagent of practical synthetic value for the preparation of this kind of imides.

In order to define the influence of the nitrogen substituents several amides (**1a-d**) of palmitic acid and cyclic and acyclic *N,N*-dialkyl amines were prepared and treated with $CrO_3$·3,5-DMP (20 eq.) at room temperature for 4 hours (Figure 1) and the reaction mixtures analyzed by $^1$H NMR. The pyrrolidine derivative **1a** was consumed after 4 hours and only the corresponding imide was obtained. The piperidine derivative **1b** showed a lower reactivity and it afforded a mixture of amide:imide (0.8:1). The acyclic *N,N*-dialkyl derivatives gave poorer results as the *N,N*-diethylderivative **1c** reacted to a lesser extent (amide:imide, 6:1) and with the

*N,N*-diallylderivative **1d** no imide was detected by NMR analysis. A similar treatment of **1a** with PCC resulted in a total recovery of unreacted starting material.

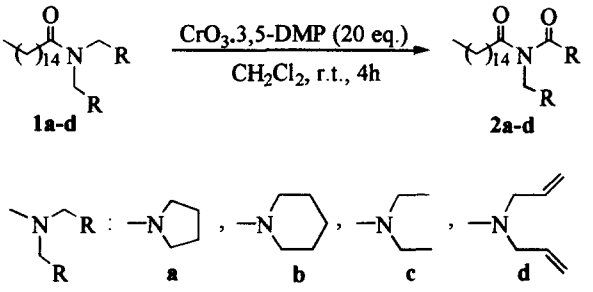



**Figure 1**

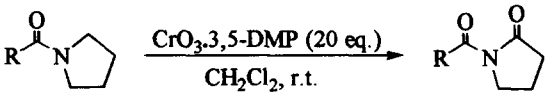
These results showed that the $CrO_3$·3,5-DMP complex was able to carry out the oxidation of *N,N*-dialkyl amides to imides and that good yields could be obtained with the *N*-acyl derivatives of pyrrolidine. In order to explore the scope of the reaction several aliphatic and aromatic *N*-acyl-pyrrolidines were tested.

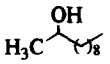
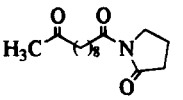
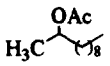
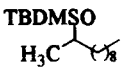
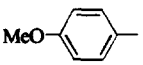
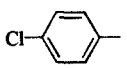
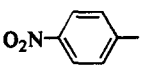
As reported in Table 1, good results were obtained with aliphatic pyrrolidino amides after 4 hours (Entries 1-6). When R is a saturated long chain (Entries 1 and 2) *ca.* 80% yields were obtained. In the presence of a methyl ester group (Entry 3) a 70% yield was obtained. When a hydroxyl group was present (Entry 4), the complex brought about the oxidation of both functions and the keto imide was obtained as the major compound (50%) together with a minor amount of the related keto amide (A) (5%). In order to test the stability of two usual hydroxyl protecting groups under the reaction conditions, the acetate and *tert*-butyldimethylsilyl derivatives of this alcohol were also prepared (Entries 5 and 6, respectively). In both cases the reaction was not complete and a little amount of starting material was recovered unaltered. The acetate derivative (Entry 5) gave an acceptable yield (59%) but with the silyl derivative (Entry 6) the yield of imide was lower (32%) as this protecting group was sensitive to the reaction conditions and the substrate suffered partial oxidation to ketone (A) (20%).

Aromatic amides (Entries 7-10) showed lower reactivity and they needed longer reaction times. The rate and yield of oxidation increased with the electron-donating ability of the substituents on the aromatic ring (MeO > H > Cl > $NO_2$) and for the less reactive amides (Entries 9 and 10) a considerable amount of unreacted starting material remained after 24 hours.

In conclusion, the $CrO_3$·3,5-DMP complex is a suitable oxidant for the transformation of *N*-acyl-pyrrolidines to *N*-acyl-pyrrolidones and it constitutes a complementary method to others previously described for the preparation of these kinds of products.

**Table 1**: Oxidation of Aliphatic and Aromatic *N*-Acyl-Pyrrolidines with $CrO_3$·3,5-Dimethylpyrazole.

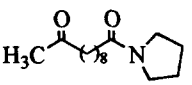



| Entry | R- | Time | Imide (%)[a] | Recovered amide (%) |
|---|---|---|---|---|
| 1 | $CH_3(CH_2)_{14}$- | 4 h | 79 | - |
| 2 | $CH_3(CH_2)_8$- | 4 h | 81 | - |
| 3 | $MeO_2C(CH_2)_3$- | 4 h | 70 | - |
| 4 |  | 4 h |  50[b] | - |
| 5 |  | 4 h | 59 | 6 |
| 6 |  | 4 h | 32[c] | 5 |
| 7 |  | 24 h | 57 | 11 |
| 8 |  | 24 h | 70 | 5 |
| 9 |  | 24 h | 50 | 17 |
| 10 |  | 24 h | 41 | 23 |

[a] Isolated yield after chromatographic purification. All compounds were characterized by IR, $^1H$ and $^{13}C$ NMR and MS.

[b] Keto amide (A) was also obtained (5%).

[c] Keto amide (A) was also obtained (20%).



(A)

**General procedure.** A solution of amide (0.8 mmol) in $CH_2Cl_2$ (4 mL) was added to a cooled (-25°C) solution of $CrO_3$·3,5-DMP[9,10] (16 mmol) in $CH_2Cl_2$ (8 mL), and the reaction mixture was stirred at room temperature (4 h or 24 h). A solution of 5 M aq. NaOH (20 mL) was added and the mixture stirred for 20 minutes. The two phase mixture was filtered through a short pad of silica gel (*ca.* 10 g) and eluted with EtOAc (*ca.* 150 mL) to ensure total recovery of the products. The organic solution was washed with aqueous 2M HCl and brine, dried over $Na_2SO_4$, concentrated and chromatographed on silica gel with hexane-EtOAc mixtures as eluent.

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## REFERENCES

1. Benz, G. in *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*, Vol 6; Trost, B. M. and Fleming I., Ed.; Pergamon Press, London 1991; p 409.
2. Sheehan, J. C.; Tulis, R. W., *J. Org. Chem.* **1974**, *39*, 2264.
3. Tangari, N.; Tortorella, V., *J. Chem. Soc. Chem. Commun.* **1975**,71.
4. Yoshifuji, S.; Tanaka; K.-I.; Kawai; T.; Nitta, Y., *Chem. Pharm. Bull.*, **1985**, *33*, 5515.
5. Tanaka, K.-I.; Yoshifuji, S.; Nitta, Y., *Heterocycles*, **1986**, *24*, 2539.
6. Tanaka, K.-I.; Yoshifuji, S.; Nitta, Y., *Chem. Pharm. Bull.*, **1987**, *35*, 364.
7. Murata, S.; Miura, M.; Nomura, M., *J. Chem. Soc. Perkin T. 1*, **1987**, 1259.
8. Masui, M.; Hara, S.; Ozaki, S., *Chem. Pharm. Bull.*, **1986**, *34*, 975.
9. Corey, E.J.; Fleet, G. W., *Tetrahedron Lett.*, **1973**, 4499.
10. Salmond, W. G.; Barta, M. A.; Havens, J. L., *J. Org. Chem.* **1978**, *43*, 2057.

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