RhCl₃-catalysed Amide Bond Formation under Mild Conditions

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Summary The reaction of carboxylic acid esters with amines is accelerated in the presence of catalytic amounts of RhCl₃.3H₂O at a reasonably low temperature; optically

active 2,5-dioxopiperazines can be synthesized in high yield from the corresponding amino-acid esters using this procedure.

ALTHOUGH a number of reactions, which involve the formation of a transition-metal alkoxide [equation (1)] as an initial step have appeared,¹ such reactions of amines are scarce [equation (2)] 1C,2 We have now found that the

$$\begin{array}{c} -M - \\ M - \\ RO - H \longrightarrow RO - M - H \end{array}$$
(1)

$$\begin{array}{c} -M - \\ | \\ RN-H \longrightarrow RN-M-H \end{array}$$

$$(2)$$

reaction of carboxylic acid esters with amines is accelerated in the presence of catalytic amounts of RhCl₃ 3H₂O (<5 mol The results are summarized in the Figure Other %) catalysts, such as RhCl(PPh₃)₃, [Rh(CO)₂Cl]₂, and RuCl₃, are less effective in amide bond formation The catalyst works well for other esters, such as ethyl formate, ethyl isovalerate, and ethyl isobutyrate, but does not work for the corresponding acids, or for esters with bulky groups such as Bu^t and Prⁱ

A mechanistic rationale which may account for the observed catalytic process is shown in the Scheme, (a) oxida tive insertion of Rh^I into the N-H bond takes place and is

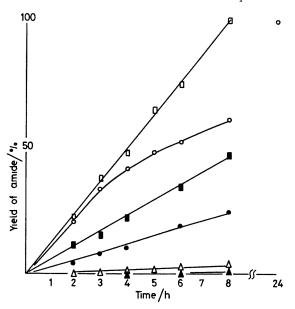


FIGURE Dependence of yield of amide on catalyst concentration at 60 °C for EtCO₂R (10 mmol) + Bu^aNH₂(30 mmol) → EtCO-NHBu^a R = Me, \triangle , No catalyst, \bigcirc , RhCl₃ 3H₂O, 1%, \square , RhCl₃ 3H₂O, 5%, R = Et, \blacktriangle , No catalyst, \bigoplus , RhCl₃ 3H₂O, 1%, \square , ■, RhCl₃·3H₂O, 5%

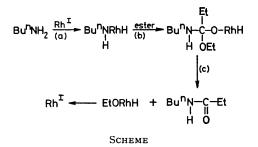
† The optical yield has not necessarily been optimized

‡ The analysis was performed at the Institute for Biological Science, Sumitomo Chemical Co , Ltd , Osaka

¹ Eg, (a) E L Muetterties, 'Transition Metal Hydrides' Marcel Dekker, New York, 1971, (b) Y Sasson and J Blum, J. Org Chem, 1975, 40, 1887, (c) M A Bennett and T Yoshida, J Am Chem Soc, 1978, 100, 1750 ² T Yamamoto, K Igarashi, J Ishizu and A Yamamoto, J Chem Soc Chem Commun, 1979, 554 ³ J Ishizu, T Yamamoto, and A Yamamoto Chem Lett, 1976, 1091

⁴ A L J Beckwith in 'The Chemistry of Amides, ed J Zabicky, Interscience, London, 1970, ch 2, p 73 ⁵ N Izumiya, S Lee, T Kanmera, and H Aoyagi, J Am Chem Soc, 1977, 99, 8346, D E Nitecki, B Halpern, and J W Westley, J Org Chem, 1968, 33, 864, E Fischer, Ber, 1906, 39, 2893 ⁶ H Poisel and U Schmidt, Chem Ber, 1972, 105, 625 To avoid racemization, it is necessary to perform the reaction at room temperature for 3 weeks

followed by (b) the addition of the N-Rh bond to the carbonyl group and (c) β -elimination and reductive elimination Alternatively the acylrhodium complex may be formed via oxidative addition of the ester³ to Rh^I



Irrespective of the precise mechanism, the present development offers some synthetic advantages The conversion of a carboxylic acid ester into an amide frequently needs high temperatures, and strongly basic or acidic conditions⁴ Activated esters, such as imide esters and p-nitrophenyl esters are required to carry out the condensation under mild conditions However, in the presence of RhCl₃ 3H₂O (1 mol %) optically active 3,6-dimethyl-2,5-dioxopiperazine (2) was obtained quantitatively from L-alanine ethyl ester (1) [equation (3)] † The isomer ratio was determined using a capillary column packed with an optically active liquid phase (OA-300), ± LL-(2) (85%), DD-(2) (5%), and LD-(2) (10%) Similarly, other aminoacid esters, such as the D-isomer of (1), phenylalanine, and value, afforded the corresponding dioxopiperazines in optically active form Normally, optically pure dioxo-

$$\begin{array}{c} \text{MeCHCO}_{2}\text{Et} & \frac{\text{RhCl}_{3} \cdot 3\text{H}_{2}\text{O}}{60} \cdot \frac{1}{\text{C}, 48\text{h}} & 0 \\ \text{NH}_{2} & \frac{1}{100} \cdot \frac{1}{\text{C}, 48\text{h}} & 1 \\ 1 - \text{L} & 2 - \text{LL} (2 - \text{DD}) & 2 - \text{LD} \end{array}$$
(3)

piperazines are prepared by the cyclization of the corresponding dipeptides ⁵ One-step syntheses from amino-acid esters at high temperature are frequently accompanied by polymerization and loss of optical activity 6 Consequently, the formation of an amide bond in essentially quantitative yield at reasonably low temperature using homogeneous catalysts such as RhCl₃ 3H₂O and RuCl₃ should prove very useful in the synthesis of certain peptides

The support by the Ministry of Education, Science and Culture (Grant-in-Aid for Special Project Research) is acknowledged

(Received, 14th May 1980, Com 526)