CHEMISTRY LETTERS, pp. 1559-1560, 1982.

FACILE SYNTHESIS OF β-KETOESTERS BY A COUPLING REACTION OF THE REFORMATSKY REAGENT WITH ACYL CHLORIDES CATALYZED BY A PALLADIUM COMPLEX

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β-Ketoesters were obtained in good yields by the reaction of the Reformatsky reagent with acyl chlorides catalyzed by a palladium complex under mild conditions.

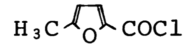
β-Ketoesters are highly versatile and useful synthetic intermediates, and have enjoyed diverse chemical preparations.$^{1)}$ Although acylation of malonic acid derivatives is the most widely exploited route in these varied syntheses, the condensation of an acetate unit with an acyl chloride seems to provide a more straightforward method. Several modifications of this type of reaction were described, e. g. the use of silylketene acetals$^{2)}$ or the treatment with a stabilized Wittig reagent$^{3)}$ to yield various β-ketoesters. It had been also considered that the Reformatsky reaction of an acyl chloride would give a very convenient route to realize β-ketoester synthesis. In previous papers,$^{4)}$ however, a successful Reformatsky type condensation of aroyl chloride had been limited to α,α-disubstituted acetate. Attempts to condense acyl chlorides with ethyl α-bromoacetate or α-bromopropionate gave poor yields of β-ketoesters, because of the further condensation of the product involving their α-hydrogen. We now wish to report the first successful direct condensation of α-unsubstituted acetate unit with an acyl chloride by the use of the Reformatsky reagent in the presence of a palladium catalyst under mild conditions.

The present Reformatsky reaction depends remarkably on the nature of palladium catalysts. Palladium(0) catalysts were found to be superior to palladium(II) catalysts. For example, in the reaction of the Reformatsky reagent with benzoyl chloride in 1,2-dimethoxyethane (DME) at 0°C for 2 h, the use of $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ as a catalyst gave ethyl benzoylacetate in 61 or 20% yield, respectively. A palladium (0) complex, prepared from $Pd(PPh_3)_2Cl_2$ and diisobutylaluminum hydride *in situ*,$^{5)}$ gave the best result of 80% yield. The results with various acyl chlorides in the presence of the Pd(0) catalyst are summarized in the Table.

$$RCOCl + BrZnCH_2CO_2Et \xrightarrow[DME]{cat.\ Pd(0)} RCOCH_2CO_2Et$$

Aromatic and heterocyclic acyl chlorides gave the corresponding β-ketoesters in over 80% yields except for the cases of *p*-nitro- and *p*-methoxybenzoyl chlorides. α,β-Unsaturated acyl chlorides such as crotonyl and cinnamoyl chlorides gave the

Table. β-Ketoester Synthesis by the Reaction of the Reformatsky Reagent with Acyl Chlorides Catalyzed by Pd(0) Complex[a]

Acyl Chloride	Yield(%)[b]	Acyl chloride	Yield(%)[b]
C_6H_5COCl	80	(*E*)-$CH_3CH=CHCOCl$	72[c]
p-ClC_6H_4COCl	90	(*E*)-$C_6H_5CH=CHCOCl$	73[c]
m-ClC_6H_4COCl	83		89[c]
p-$CH_3C_6H_4COCl$	84	$CH_3(CH_2)_7COCl$	30[d]
p-$NO_2C_6H_4COCl$	41	$(CH_3)_2CHCOCl$	24[d]
p-$CH_3OC_6H_4COCl$	51	$(CH_3)_3CCOCl$	29[d]

[a] All reactions were carried out in 1 mmol scale with the same procedure as described in the text. All products were identified by IR and NMR spectra. [b] Isolated yields by silica gel TLC based on acyl chlorides. [c] Two mol% of Pd(0) complex was used. [d] The reaction of acyl chlorides with ethyl bromoacetate was carried out in the presence of zinc and 5 mol% of $Pd(PPh_3)_4$ under reflux in DME for 1 h.

desired β-ketoesters in good yields. The reaction of nonanoyl chloride, however, gave a poor result (12%). In the cases of aliphatic acyl chlorides, slightly improved results were obtained by the treatment of the acyl chlorides with ethyl bromoacetate in the presence of zinc and 5 mol% of $Pd(PPh_3)_4$ in DME under reflux for 1 h.[6)]

A typical procedure for the preparation of ethyl benzoylacetate using this coupling reaction is as follows: The Reformatsky reagent (2.5 ml of 0.88M solution in DME, 2.2 mmol), prepared from ethyl α-bromoacetate and zinc powder,[7)] was added dropwise into a suspension of Pd(0) complex (Pd-DIBAL,[5)] 1 mol%) and benzoyl chloride (1.0 mmol) in DME (5 ml) at 0 °C, and the reaction mixture was stirred for 2 h at this temperature. The reaction was quenched by the addition of 2M hydrochloric acid solution, and the organic layer was extracted with ether. Purification by TLC on silica gel gave ethyl benzoylacetate in 80% yield.

Thus, the present method has some characteristics of easy operation under mild conditions for the preparation of β-ketoesters.

References

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6) The use of the preformed Reforrmatsky reagent was necessary in the reaction of aromatic acyl chlorides. The reaction of benzoyl chloride with ethyl bromoacetate in the presence of zinc and a Pd(0) catalyst gave many products which were difficult to separate.
7) The Reformatsky reagent was prepared quantitatively according to the procedure of Gaudemar *et al.*[8)] in dimethoxymethane. The solvent was removed under a reduced pressure and then the resulting reagent was dissolved in DME.
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(Received July 26, 1982)