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Ruthenium-catalyzed Reductive Alkylation of Active Methylene Compounds with Aldehydes under Synthesis Gas

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Active methylene compounds undergo reductive alkylation with aldehydes when heated at 135-230 °C under synthesis gas of 100 atm in the presence of ruthenium carbonyl.

Although alkylation of active methylene compounds is readily carried out through in situ generation of carbanions and their reaction with electrophiles,1) reductive alkylation with carbonyl compounds would be an alternative method which warrants further studies from the industrial viewpoint. Several patents have disclosed that heterogeneous catalysis by palladium occasionally in conjunction with a variety of promotors is effective for the latter transformation.2-5) As to homogeneous catalysis, however, only the use of rhodium chloride-base systems under the water gas shift reaction conditions has been reported.6) On the other hand, carbonylferrates are known to promote the transformation with a wide range of aldehydes, but the reaction is not catalytic.7) We now report the first successful reductive alkylation of active methylene compounds in the presence of ruthenium carbonyl used as the catalyst.

$$RCH_2Z + R'CHO \xrightarrow[-H_2O]{H_2\ (CO)} RCH(CH_2R')Z \quad \text{(Z: electron-withdrawing group)}$$

In a typical experiment, a 40 ml autoclave was charged with phenylacetonitrile (4.0 mmol), paraformaldehyde (16 mmol as CH_2O unit), $Ru_3(CO)_{12}$ (6.7×10^{-3} mmol), and dimethylformamide (2 ml), pressurized with synthesis gas of 100 atm ($CO/H_2 = 1$), and was heated at 230 °C for 16 h. GC analysis revealed the formation of 2-phenylpropionitrile in nearly quantitative yield. The reaction mixture was poured into ether, washed with water, and was distilled (Kugelrohr) at 120 °C/10 mmHg to afford 451 mg of pure sample (86% isolated yield), which was fully characterized by IR, NMR, and MS fragmentation patterns with reference to an authentic sample.

As Table 1 shows, ruthenium carbonyl under synthesis gas is an efficient catalyst for the reductive alkylation. In particular, active methylene compounds which have two electron-withdrawing groups react with aliphatic aldehydes (paraformaldehyde and butyraldehyde) to give excellent yields of mono-alkylation products. The reaction with benzaldehyde was slower than the others. Acetophenone and cyclohexanone underwent not only mono- but also dimethylation with paraformaldehyde. Selectivity to dimethylation was considerably improved by increasing the reaction time and the amount of the aldehyde. The reaction pathway of the present reductive alkylation presumably involves aldol type condensation between the substrate and aldehyde,[8)] dehydration, and hydrogenation of the resulting olefinic bond. In the reaction of methyl cyanoacetate, acetonitrile and propionitrile were formed as byproducts. Likewise, methyl propionate was detected in the reaction of malonate. The formation of these byproducts may be due to hydrolysis of the substrate and product with the water coming from the dehydration process followed by decarboxylation.

$$RCH_2Z + R'CHO \longrightarrow RCHZ\text{-}CHR'(OH)$$

$$\xrightarrow{-H_2O} RCZ{=}CHR' \xrightarrow{H_2} RCH(CH_2R')Z$$

Under the present conditions, $RuCl_2(CO)_3$, $RuCl_2(PPh_3)_3$, $Fe_3(CO)_{12}$, and

$Co_2(CO)_8$ were much less active, and $Rh_4(CO)_{12}$ and $RhCl(PPh_3)_3$ were totally inactive for the reaction of acetophenone. Thus, $Ru_3(CO)_{12}$ has been proved to be the best catalyst.

Table 1. Ruthenium Carbonyl-catalyzed Reductive Alkylation of Active Methylene Compounds with Aldehydes under Synthesis Gas[a)]

Substrate	Alde-hyde	Temp °C	Time h	Product	Yield[b)] %
$PhCH_2CN$	HCHO[c)]	230	16	$PhCH(CH_3)CN$	100 (86)
$p\text{-}(i\text{-}C_4H_9)C_6H_4CH_2CN$	HCHO[c)]	230	16	$p\text{-}(i\text{-}C_4H_9)C_6H_4CH(CH_3)CN$	100
$CH_2(CN)_2$	HCHO	150	16	$CH_3CH(CN)_2$	81
$CH_2(CN)COOCH_3$	HCHO	135	4	$CH_3CH(CN)COOCH_3$[d)]	87
$CH_2(COOCH_3)_2$	HCHO	135	4	$CH_3CH(COOCH_3)_2$[e)]	73
$CH_2(COCH_3)_2$	HCHO	150	16	$CH_3CH(COCH_3)_2$	84
$CH_2(COCH_3)_2$	C_3H_7CHO[f)]	150	16	$C_4H_9CH(COCH_3)_2$	89
$CH_2(COCH_3)_2$	PhCHO	150	16	$PhCH_2CH(COCH_3)_2$	29
$PhCOCH_3$	HCHO[c)]	150	16	$PhCOC_2H_5$	22
				$PhCOCH(CH_3)_2$	28
$PhCOCH_3$	HCHO[g)]	150	40	$PhCOC_2H_5$	7
				$PhCOCH(CH_3)_2$	51
$\overline{(CH_2)_5CO}$[h)]	HCHO	230	16	$\overline{(CH_2)_4COCH}CH_3$[i)]	33
				$\overline{(CH_2)_3CH(CH_3)COCH}CH_3$	10

a) $Ru_3(CO)_{12}$ 6.7 × 10^{-3} mmol, active methylene compound 4 mmol, aldehyde 4 mmol, DMF 2 ml. b) GC yield (isolated yield in parenthesis). c) 16 mmol. d) Other products: CH_3CN 3%, C_2H_5CN 5%. e) Other product: C_2H_5-$COOCH_3$ 1%. f) 5 mmol. g) 64 mmol. h) N-Isopropylpyrrolidone (2 ml) was used as the solvent. i) Other products: cyclohexanol 9%, 2-methylcyclohexanol 12%.

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8) Although ruthenium-catalyzed aldol condensation has been reported, we do not believe that ruthenuim species generated under the present conditions play an important role in the aldol condensation step which we suppose to be involved in the reductive alkylation process. See T. Naota, H. Taki, M. Mizuno, and S. -i. Murahashi, J. Am. Chem. Soc., 111, 5954 (1989).

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