Tetrahedron Letters,Vol.27,No.39,pp 4745-4748,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ACYLATION OF ACTIVE METHYLENE COMPOUNDS VIA PALLADIUM COMPLEX-CATALYZED CARBONYLATIVE CROSS-COUPLING OF ORGANIC HALIDES

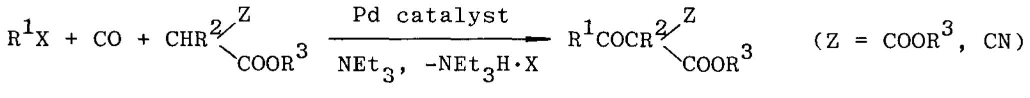
Toshi-aki Kobayashi and Masato Tanaka*

National Chemical Laboratory for Industry, Yatabe, Ibaraki 305, Japan

Summary: New procedures for acylation of active methylene compounds via palladium complex-catalyzed carbonylation of organic halides are disclosed.

Carbonylation of organic halides with molecular hydrogen or nucleophiles (water, alcohols, and amines) smoothly proceeds and constitutes a useful and industrially-important method for the synthesis of carboxylic acid derivatives. Since we reported the first successful examples of carbonylative cross-coupling of halides with carbon nucleophiles which gave various unsymmetrical ketones,[1] much effort has been focused on exploration for variations in this area.[2] However, with the exception of our finding of acetylenic ketone synthesis based on the carbonylative cross-coupling of halides and terminal acetylenes,[1d] there is no paper on the carbonylation of halides with carbon acids. Successful extentions to active methylene compounds are disclosed in this communication.

Iodobenzene (1.88 mmol) and diethyl methylmalonate (2.0 mmol) in triethylamine (2 ml) were reacted with carbon monoxide (20 atm) at 120°C in the presence of a catalytic amount of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (1.88×10^{-2} mmol). Glc analysis of the resulting mixture revealed the formation of diethyl methylbenzoylmalonate in 75.3% yield. The mixture was filtered and distilled (Kugelrohr) to give the pure sample (61% isolated yield, bp 120°C/0.1 torr).



$$R^1X + CO + CHR^2\left\langle\begin{matrix}Z\\ COOR^3\end{matrix}\right. \xrightarrow[NEt_3,\ -NEt_3H\cdot X]{\text{Pd catalyst}} R^1COCR^2\left\langle\begin{matrix}Z\\ COOR^3\end{matrix}\right. \quad (Z = COOR^3,\ CN)$$

Table 1 summarizes the results obtained through similar procedures. The yields have not been optimized. In the reactions of diethyl and diisopropyl malonate, the mono-benzoylation products (benzoylmalonates) once formed were prone to further undergo *O*-benzoylation to give the double-benzoylation products. However, the mono-benzoylation product was obtained in the reaction of ethyl cyanoacetate, though the yield was low. As was anticipated, ethyl acetoacetate exclusively gave the *O*-benzoylation product. *O*-Benzoylation was also observed for 1,2-diphenylethanone and acetophenone. Other active methylene

Table 1 Carbonylative cross-coupling of organic halides with carbon acids in triethylamine[a]

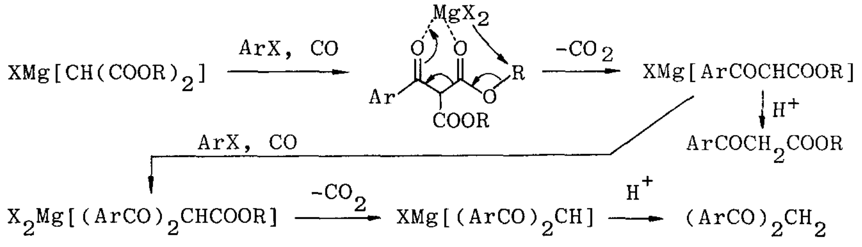
Halides	Carbon acid	Catalyst	Temp (°C)	Time (h)	Conv[b] (%)	Product	Yield[c] (%)
C_6H_5I	$CH_3CH(COOC_2H_5)_2$	$PdCl_2(DPPF)$[d]	120	33	100	$C_6H_5COC(CH_3)(COOC_2H_5)_2$	75.3 (61)
C_6H_5I	$CH_3CH(COOC_2H_5)_2$	$PdCl_2(PPh_3)_2$	120	22	83	$C_6H_5COC(CH_3)(COOC_2H_5)_2$	55.1
C_6H_5I	$CH_3CH(COOC_2H_5)_2$	$PdCl_2(SbPh_3)_2$	120	50	49	$C_6H_5COC(CH_3)(COOC_2H_5)_2$	46.8
C_6H_5I[e]	$CH_2(COOC_2H_5)_2$	$PdCl_2(DPPF)$	120	33	100	$(C_6H_5COO)(C_6H_5)C{=}C(COOC_2H_5)_2$	(73)
C_6H_5I	$CH_2[COOCH(CH_3)_2]_2$	$PdCl_2(DPPF)$	120	18	100	$(C_6H_5COO)(C_6H_5)C{=}C[COOCH(CH_3)_2]_2$	(72)
C_6H_5I	$CH_2(CN)(COOC_2H_5)$	$PdCl_2(DPPF)$	120	6	100	$(C_6H_5)(HO)C{=}(CN)(COOC_2H_5)$	(30)
C_6H_5I	$CH_3COCH_2COOC_2H_5$	$PhPdI(PPh_3)_2$	100	17	nd	$(C_6H_5COO)(CH_3)C{=}CHCOOC_2H_5$	(33)
C_6H_5I[f]	$C_6H_5COCH_2C_6H_5$	$PdCl_2(DPPF)$	120	60	100	$(C_6H_5COO)(C_6H_5)C{=}CHC_6H_5$	(95)[g]
C_6H_5I[h]	$C_6H_5COCH_3$	$PhPdI(PPh_3)_2$	120	44	100	$(C_6H_5COO)(C_6H_5)C{=}CH$	10.5[i]
C_6H_5Br	$CH_3CH(COOC_2H_5)_2$	$PdCl_2(DPPF)$	120	44	75	$C_6H_5COC(CH_3)(COOC_2H_5)_2$	65.3 (63)
p-$IC_6H_4COOC_2H_5$	$CH_3CH(COOC_2H_5)_2$	$PdCl_2(DPPF)$	120	18	100	p-$H_5C_2OOCC_6H_4COC(CH_3)(COOC_2H_5)_2$	68.5 (56)
p-IC_6H_4Cl	$CH_3CH(COOC_2H_5)_2$	$PdCl_2(DPPF)$	120	17	100	p-$ClC_6H_4COC(CH_3)(COOC_2H_5)_2$	80.9 (61)
2-C_4H_3SI[j]	$CH_3CH(COOC_2H_5)_2$	$PdCl_2(DPPF)$	120	18	100	$(2$-$C_4H_3S)COC(CH_3)(COOC_2H_5)_2$	(4)[k]
$C_6H_5CH{=}CHBr$	$CH_3CH(COOC_2H_5)_2$	$PdCl_2(DPPF)$	120	12	84	$C_6H_5CH{=}CHCOC(CH_3)(COOC_2H_5)_2$	35.7[l] (28)

[a] Effected under 20 atm of CO using 1.88 mmol halides, 2.00 mmol of carbon acids, 1.88×10^{-2} mmol of catalysts in 2 ml of triethylamine. [b] Conversion refers to the consumption of halides. [c] Glc yield based on the amount of halides charged. Figures in parentheses are isolated yields. [d] DPPF = 1,1'-bis(diphenylphosphino)ferrocene. [e] C_6H_5I charged was 4.17 mmol. [f] C_6H_5I charged was 4.8 mmol. [g] Based on 1,2-diphenylethanone charged. *N*,*N*-Diethylbenzamide was also formed (37.5% yield based on C_6H_5I charged). [h] C_6H_5I charged was 4.0 mmol. [i] Based on acetophenone charged. *N*,*N*-Diethylbenzamide was also formed (42.0% based on C_6H_5I charged). [j] 2-Iodothiophene. [k] *N*,*N*-Diethylthiophene-2-carboxamide and di-2-thienyl ketone were also formed in 23.6 and 56.6% yield, respectively. [l] *N*,*N*-Diethylcinnamamide was also formed (20.0%).

compounds such as indene, diphenylmethane, and ethyl phenylacetate were not benzoylated at all under similar conditions. We could extend the reaction with diethyl methylmalonate to bromobenzene, substituted iodobenzenes, and β-bromostyrene. In some of these reactions, *N*,*N*-diethylbenzamide was formed as a byproduct which resulted from the cleavage of triethylamine.[3]

When iodobenzene was allowed to react with pre-formed magnesium enolates of active methylene compounds, different types of products were obtained (after acidification). Thus, iodobenzene (2.0 mmol) and bromomagnesium enolate of diisopropyl malonate (4.0 mmol) in ether-benzene (1 : 1) mixture (2 ml) were exposed to carbon monoxide (20 atm) in the presence of iodophenylbis(triphenylphosphine)palladium (1.88 × 10^{-2} mmol) at 120°C for 5 h. The resulting mixture was poured into aqueous hydrochloric acid, and was extracted with ether. Glc analysis showed that isopropyl benzoylacetate was formed in 77.5% yield. Evaporation of the ether layer and distillation (Kugelrohr) gave an analytically pure sample (63.0% isolated yield, bp 122°C/1.0 torr). The results of other reactions are summarized in Table 2. Ethoxymagnesium enolate of diethyl malonate reacted similarly, though ethyl benzoate was also formed presumably due to the reaction of the ethoxy group originally bound to magnesium. However, when the reaction of magnesium enolate of diethyl malonate was effected under forcing conditions, the yield of benzoylacetate decreased, and instead, dibenzoylmethane became the main product. The reaction of the enolate of ethyl acetoacetate also gave the corresponding β-diketone. For the β-keto esters and/or β-diketones to be formed, decarbalkoxylation must intervene during the progress of the reaction. We do not have any evidence for the decarbalkoxylation mechanism. However, the magnesium halide-assisted decarbalkoxylation[4] seems to rationalize the results as follows:

$$ArX + CO + XMg[CH(COOR^3)_2] \xrightarrow[2)\ H^+]{1)\ \text{Pd catalyst}} ArCOCH_2COOR^3 \text{ and/or } (ArCO)_2CH_2$$



(X = Br, I, or EtO)

In summary, the present paper offers the new method for acylation of active methylene compounds via carbonylation with organic halides. The new method will be useful when acid halides are not readily accessible.

Table 2 Carbonylative cross-coupling of iodobenzene with magnesium enolate[a]

Magnesium enolate	Temp (°C)	Time (h)	Conv[b] (%)	Product	Yield[c] (%)
$BrMgCH[COOCH(CH_3)_2]_2$ [d,e]	120	5	81	$C_6H_5COCH_2COOCH(CH_3)_2$	77.5 (63)
$(C_2H_5O)MgCH(COOC_2H_5)_2$ [f]	100	8	nd	$C_6H_5COCH_2COOC_2H_5$ $C_6H_5COOC_2H_5$	71.5 (67) ~20
$BrMgCH(COOC_2H_5)_2$ [d]	90 ↓ 120	21 + 4	98	$C_6H_5COCH_2COOC_2H_5$ $(C_6H_5CO)_2CH_2$	18.4 (17) 78.8 (60)
$(C_2H_5O)MgCH(COCH_3)(COOC_2H_5)$ [f]	100	18	nd	$C_6H_5COCH_2COCH_3$ $C_6H_5COOC_2H_5$	(31) ~20

[a] Effected under 20 atm of CO using 2.0 mmol of C_6H_5I, 2.1 mmol of enolates, 1.88×10^{-2} mmol of $PhPdI(PPh_3)_2$ in 2 ml of the solvent. [b] Conversion refers to the consumption of iodobenzene. [c] Glc yield based on C_6H_5I charged. The figures in parentheses are isolated yields. [d] Benzene-ether (1 : 1) solvent. [e] Enolate charged = 4.0 mmol. [f] Benzene solvent.

References

1 a) M. Tanaka, Tetrahedron Lett., 1979, 2601. b) M. Tanaka, Synthesis, 1981, 47. c) T. Kobayashi and M. Tanaka, J. Organomet. Chem., 205, C27 (1981). d) T. Kobayashi and M. Tanaka, J. Chem. Soc., Chem. Commun., 1981, 333; M. Tanaka, T. Kobayashi, and T. Sakakura, Nippon Kagaku Kaishi, 1985, 537. e) M. Tanaka, Bull. Chem. Soc. Jpn., 54, 637 (1981).

2 a) N. A. Bumagin, I. G. Bumagina, A. N. Kashin, and I. P. Beletskaya, Izv. Akad. Nauk USSR, Ser. Khim., 1981, 1675. b) N. A. Bumagin, I. G. Bumagina, A. N. Kashin, and I. P. Beletskaya, Dokl. Akad. Nauk USSR, 261, 1141 (1981). c) V. P. Baillargeon and J. K. Stille, J. Am. Chem. Soc., 105, 7175 (1983). d) Y. Tamaru, H. Ochiai, Y. Yoshimi, and Z. Yoshida, Tetrahedron Lett., 24, 3869 (1983). e) N. A. Bumagin, Y. V. Gulevich, and I. P. Beletskaya, Izv. Akad. Nauk USSR, Ser. Khim., 1984, 953. f) J. H. Meerfield, J. P. Godschalx, and J. K. Stille, Organometallics, 3, 1108 (1984). g) F. K. Sheffy, J. P. Dodschalx, and J. K. Stille, J. Am. Chem. Soc., 106, 4833 (1984). h) Y. Tamaru, H. Ochiai, and Z. Yoshida, Tetrahedron Lett., 25, 3861 (1984). i) N. A. Bumagin, Y. V. Gulevich, and I. P. Beletskaya, J. Organomet. Chem., 285, 415 (1985). j) N. A. Bumagin, A. B. Ponomaryov, and I. P. Beletskaya, Tetrahedron Lett., 26, 4819 (1985). k) N. A. Bumagin, Y. V. Gulevich, and I. P. Beletskaya, J. Organomet. Chem., 282, 421 (1985). l) Y. Wakita, T. Yasunaga, M. Kojima, J. Organomet. Chem., 288, 261 (1985). m) J. -B. Verlhac, E. Chanson, B. Jousseaume, J. -P. Quintard, Tetrahedron Lett., 26, 6075 (1985).

3 T. Kobayashi and M. Tanaka, J. Organomet. Chem., 231, C12 (1982).

4 Y. Tsuda and Y. Sakai, Synthesis, 1981, 119.

(Received in Japan 12 June 1986)