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Synthesis of Pyridylglyoxylic Acid Derivatives via a Palladium-Catalysed Double Carbonylation of Iodopyridines

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Abstract: 4-Iodopyridines react with CO and $HNEt_2$ or 2-BuOH/NEt_3 in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ to give the corresponding α-keto amides and esters in fair to high yields.

The palladium-catalysed double carbonylation of aryl halides to give α-keto acids, esters and amides has been extensively studied.[1] There have been however very few applications to the synthesis of fine chemicals.[1c] In an ongoing project aimed at developing a new synthesis of camptothecine, we required compounds of type **D3**, which can be envisioned by double carbonylation of the parent iodo compound (**S3**). The scarce informations available about related reactions suggest poor efficiency.[2] We now report that such a double carbonylation of 4-iodopyridines provides an efficient entry to 4-pyridylglyoxylic acid derivatives, compounds which are not easily attainable via classical organic synthesis.

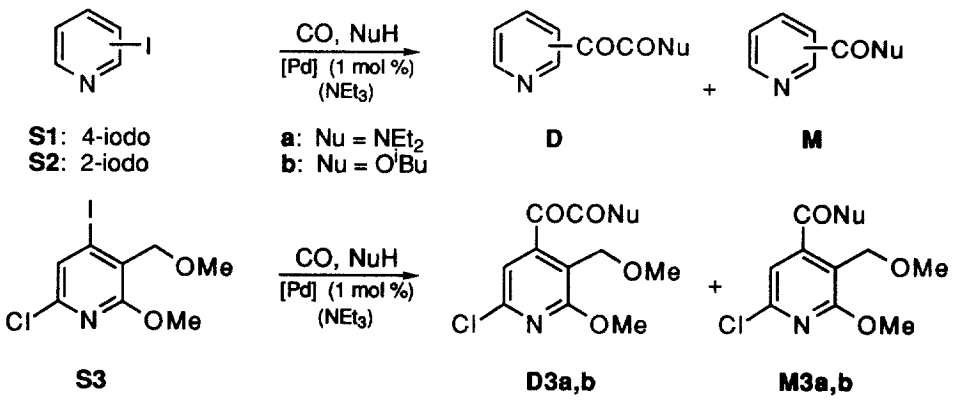

Table 1 summarises selected results of the reactions of two model iodopyridines and of **S3**[3] under various conditions. α-Keto amides of 4-iodopyridines **S1** and **S3** are obtained in more than 90% yield under smooth conditions, provided temperature, CO pressure, amine concentration, catalyst precursor and solvent are adequately adjusted. A typical procedure is as follows (entry 5): a solution of **S1** (0.50 g, 2.44 mmol), $HNEt_2$ (1.2 mL, 12 mmol), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol) and PCy_3 (19.2 mg, 0.072 mmol) in CH_2Cl_2 (30 mL) was charged under nitrogen into a 60 mL-stainless steel autoclave equipped with a magnetic stirrer bar. After sealing, the reactor was pressurised to 60 bar with carbon monoxide and heated

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to 50 °C for 6 h. After cooling to room temperature, the solution was analyzed by GLC, which showed that *N,N*-diethyl-4-pyridylglyoxylamide (**D1a**) had been formed in 95% yield along with *N,N*-diethyl-4-nicotamide (**M1a**) in 5% yield. After concentration of the solution under vacuum, the crude product was chromatographed on silica using EtOH/AcOEt/heptane (2:2:1) as eluent, to give the analytically pure glyoxylamide (0.45 g, 90% yield).[4]

α-Keto esters of 4-iodopyridines **S1** and **S3** are also produced in moderate yields (entries 6 and 11), although it is noteworthy that "optimal" reaction conditions are much more narrow than for the synthesis of α-keto amides. The reactions of 2-iodopyridine (**S2**) are less selective (entries 7 and 8).

Table 1. Palladium-catalysed double carbonylation of iodopyridines **S1-3**

Entry	Subst.	NuH	catalyst precursor	*T* (° C)	Time[a] (h)	S conv (%)[b]	D sel (%)[b]
1	**S 1**	**a**	$PdCl_2(PPh_3)_2$	50	6	100	50
2	"	"	$PdCl_2(PPhMe_2)_2$	"	28	100	61
3	"	"	$PdCl_2(PPh_2Me)_2$	"	30	25	>99
4	"	"	$Pd(dba)(PCy_3)_2$	"	6.5	100	93
5	"	"	$Pd(OAc)_2$ + 3 PCy_3	"	6	100	95 (90)
6[c]	"	**b**	$Pd(dba)(PCy_3)_2$	"	48	100	72 (60)
7	**S 2**	**a**	"	"	3.5	100	54
8[c]	"	**b**	"	70	140	78	16
9	**S 3**	**a**	$PdCl_2(PPh_3)_2$	40	31	100	75
10	"	"	$Pd(dba)(PCy_3)_2$	"	20	98	93 (82)
11[c]	"	**b**	"	50	22	100	31

[a] The reaction time was not optimised. [b] Determined by quantitative GLC; figures in brackets are isolated yields. Compound **M** accounts for the balance. [c] **S** (2.44 mmol), 2-BuOH (3 mL), NEt_3 (2 mL), Pd 2 mol%, CH_2Cl_2 (25 mL), 90 bar CO.

References and Notes

1. Leading references: (a) Tanaka, M.; Kobayashi, T.-A.; Sakakura, T. *J. Chem. Soc., Chem. Commun.* **1985**, 837. (b) Sakakura, T.; Yamashita, H.; Kobayashi, T.-A.; Hayashi, T.; Tanaka, M. *J. Org. Chem.* **1987**, *52*, 5733. (c) Ozawa, F.; Yanagihara, H.; Yamamoto, A. *J. Org. Chem.* **1986**, *51*, 415.
2. (a) Ketoamidocarbonylation of 3-bromopyridine proceeds in 58% yield and selectivity at total conversion: Ozawa, F.; Soyama, H.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1982**, *23*, 567. (b) The α-ketoester of 2-iodoquinoline is formed in 22% yield and selectivity: Ozawa, F.; Kawazaki, N.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1985**, 567.
3. Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10972.
4. All products were characterized by ^1H and $^{13}C\{^1H\}$ NMR, MS, IR and elemental analysis, and are consistent with the proposed structures. Selected data for **D3a**: ^1H NMR ($CDCl_3$): δ 7.37 (s, 1H), 4.50 (s, 2H), 3.92 (s, 3H), 3.40 (2q, *J* = 7 Hz, 2 × 2H), 3.23 (s, 3H), 1.25 (t, 3H, *J* = 7 Hz), 1.17 (t, 3H, *J* = 7 Hz). $^{13}C\{^1H\}$ NMR: δ 189.2, 163.6, 160.9, 147.9, 147.6, 117.9, 116.5, 65.8, 58.5, 54.7, 42.5, 40.3, 14.2, 12.4. MS (EI, 70 eV): 314 (M^+, 4%), 214 (61%), 186 (18%), 100 (100%).