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PALLADIUM-CATALYZED COUPLING REACTIONS OF TRIFLUOROACETIMIDOYL IODIDES WITH OLEFINS AND 1- ALKYNES

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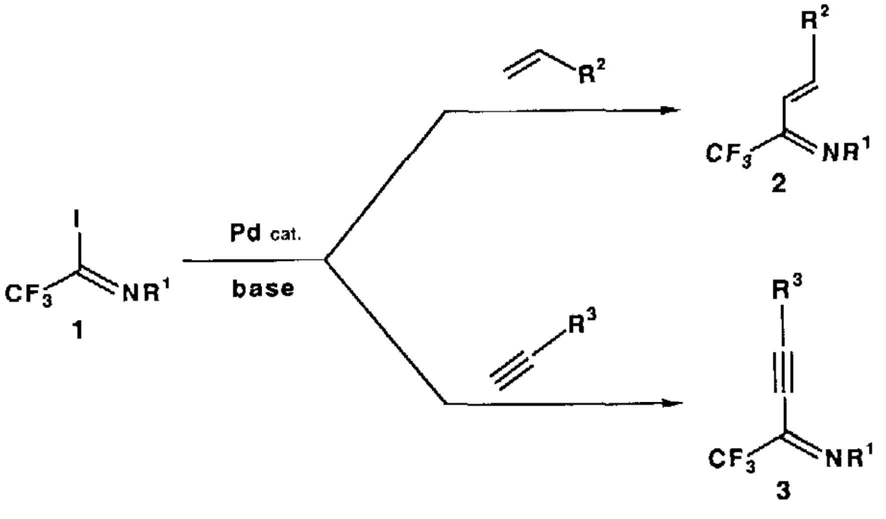
Summary; Palladium-catalyzed coupling of trifluoroacetimidoyl iodides with olefins and 1-alkynes affords trifluoromethylated α, β-unsaturated imines, which are transformed into nitrogen heterocycles bearing CF_3-group.

Methods for the synthesis of trifluoromethylated compounds have received a growing interest in the recent years, because many of these compounds exhibit interesting biological activity and high performance in material science.1) Therefore, development and transformation of trifluoromethylated building blocks are the important synthetic needs in this area.2) Trifluoroacetimidoyl chlorides3) have been found to be useful synthetic blocks for trifluoromethylated heterocycles. They behave as imidoyl carbocation and displace chlorine with both carbon 4) and nitrogen nucleophiles.5) No reaction with electrophiles has been known so far. Here we describe palladium-catalyzed coupling reactions of trifluoroacetimidoyl iodides (**1**) with active olefins (Heck type reaction) and 1-alkynes, providing the trifluoromethylated α, β-unsaturated imines which should be potential precursors of nitrogen heterocycles bearing CF_3-group.

Very few is known about Heck type reaction with imidoyl halides although numerous Pd-catalyzed coupling reactions of aryl and vinyl halides with olefins and 1-alkynes have been reported.6) Recently,

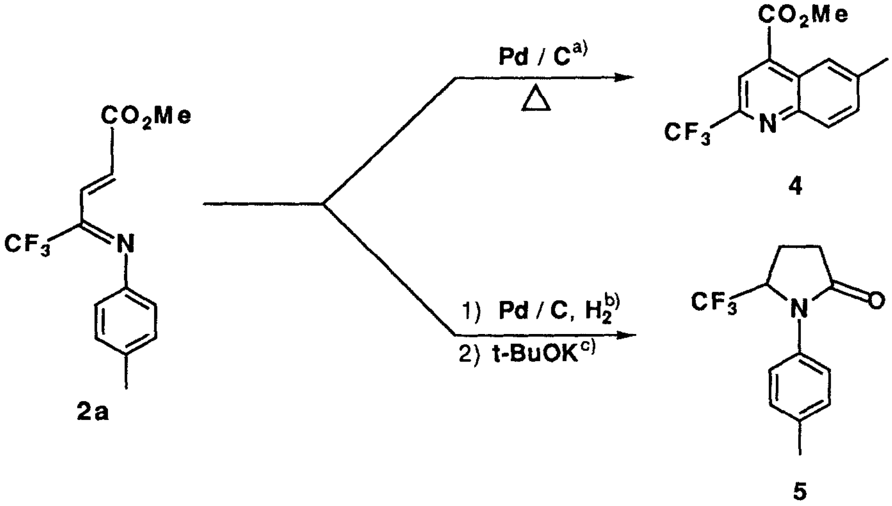


Tanaka, and Kosugi and Migita reported the Pd-catalyzed coupling reaction of benzimidoyl chlorides with alkenyl- and alkynylstannanes.[7] Although this procedure provided the coupling products in reasonable yields, it necessitated activation of olefins and 1-alkynes by stannilation.

We have found that N-aryl trifluoroacetimidoyl iodides (**1**) [8] undergo smooth palladation with $Pd_2(dba)_3 \cdot CHCl_3$ although the corresponding chlorides are recovered intact in the same conditions. During the palladation process elimination of β-fluorine did not occur[9] and coupling of **1** with olefins and 1-alkynes afforded **2** and **3** in good yields in the presence of 5 mole % equivalent of palladium catalyst. The results are summarized in Table-1.[10]

1- Alkynes react faster than the corresponding 1- alkenes (entry 1 and 10, 6 and 12). Activated carbon-carbon double bond reacts smoothly (entry 1~ 4), but non-activated olefin such as 1- octene provides the desired product in a poor yield (48%), while 1- hexyne reacts satisfactorily although the reaction rate is slower than those of the activated alkynes (entry 9 and 10). The ^{1}H-NMR revealed that the geometries of carbon-carbon double bond of **2** were trans.

The α, β-unsaturated imines **2** and **3** are promising building blocks for the trifluoromethylated nitrogen heterocycles. Thus, **2a** (R^1 = p-tolyl, R^2 = CO_2Me) was subjected to the palladium-catalyzed cyclization-dehydrogenation reaction, affording quinoline carboxylic acid ester (**4**)[11] [12] in a quantitative yield. The same compound (**2a**) was hydrogenated with Pd / C and then lactamized with t-BuOK to give the lactam (**5**)[12] in 91 % yield.



a) at 190-200 °C in nitrobenzene for 5 hr.

b) Pd/C in MeOH at room temperature for 1 day, H_2(3 atm.).

c) t-BuOK(1 equiv to **2a**) in DMF at room temperature for 10 min.

We are currently trying to apply these coupling reactions to the syntheses of heterocycles and amino acids bearing trifluoromethyl groups.

Table-1. Pd-Catalyzed Coupling of Trifluoroacetimidoyl iodides (**1**) with Olefins[a] and 1-Alkynes.[b]

entry	R^1	R^2 or R^3 (equiv)		time (hr)	temp (°C)	yield of **2** or **3** [c] (%)
1	p-$CH_3C_6H_4$	CO_2Me	(3)	31	60	**2a** (94)
2	p-$CH_3C_6H_4$	Ph	(3)	26	65	**2b** (95)
3	p-$CH_3C_6H_4$	CN	(3)	45	65	**2c** (71)[d]
4	p-$CH_3C_6H_4$	SO_2Ph	(2)	17	65	**2d** (54)
5	p-$CH_3C_6H_4$	$(CH_2)_5CH_3$	(3)	42	65	**2e** (48)[e]
6	o-BrC_6H_4	CO_2Me	(2)	48	65	**2f** (54)
7	p-$MeOC_6H_4$	CO_2Me	(3)	52	65	**2g** (86)
8	p-$CH_3C_6H_4$	CH_2OCOPh	(1.1)	12	r.t.	**3a** (70)
9	p-$CH_3C_6H_4$	$(CH_2)_3CH_3$	(2)	24	r.t.	**3b** (71)
10	p-$CH_3C_6H_4$	CO_2Et	(1.1)	2	r.t.	**3c** (66)
11	p-$CH_3C_6H_4$	Ph	(1.1)	1	65	**3d** (92)
12	o-BrC_6H_4	CO_2Et	(1.1)	4	r.t.	**3e** (47)

a) In a typical experimental procedure, a two-necked flask fitted with a septum cap, stir bar and condenser topped with a nitrogen inlet was charged with 0.017g(0.016 mmol) of $Pd_2(dba)_3 \cdot CHCl_3$, 0.088g(0.64 mmol) of K_2CO_3, and 0.2 ml of toluene. Then, 0.086ml(0.96 mmol) of methyl acrylate and 0.1g(0.32 mmol) of 2, 2, 2-trifluoroacetimidoyl iodide (**1**) in 0.5 ml of toluene were added to the catalyst mixture through a syringe. The mixture was stirred and filtered with florisil column (CH_2Cl_2). After evaporation of the solvent, the residue was purified by silica gel column chromatography to give 0.081g(94 %) of **2a**. b) A typical experimental procedure is similar to that described except that $PdCl_2$ (0.05 mol%), PPh_3 (0.1 mol%), and CuI (0.02 mol%) as catalysts and a mixture of CH_3CN and toluene(1:1) as solvents were employed. c) Isolated yield based on **1**. d) The ratio (E/Z) is 3/1. e) mixture of isomers.

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8) N-Arylacetimidoyl iodides (1) are prepared by displacement of chlorine of N-arylacetimidoyl chlorides with iodine in NaI-acetone system (yield 91 %).

9) A facile elimination of fluoride from β-metalated trifluoro-compounds is well known. T.Nakai, K. Tanaka, and N. Ishikawa, *Chem. Lett.*, 1263, (1976).

10) Structures of **2**, **3**, **4**, and **5** are identified by spectroscopic analyses (^{1}H, ^{13}C, and ^{19}F-NMR, IR, and MS).

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12) **4**: IR (Nujol, cm^{-1}) 1738 (CO_2Me); ^{1}H-NMR (δ, $CDCl_3$) 8.62 (s, 1H), 8.21 (s, 1H) 8.18 (d, J=10.2Hz,1H), 7.72 (dd, J_1=8.7Hz, J_2=1.9Hz, 1H), 4.08 (s, 3H), 2.63 (s, 3H); ^{19}F-NMR (δ, $CDCl_3$, C_6F_6) 94.28 (s). **5**: IR (Nujol, cm^{-1}) 1698 ($CONR_2$); ^{1}H-NMR (δ, $CDCl_3$) 7.20 (br.s, 4H), 4.48~4.65 (m, 1H), 2.23~2.88 (m, 4H), 2.35 (s, 3H); ^{19}F-NMR (δ, $CDCl_3$, C_6F_6) 86.58 (d, J=6.9Hz).

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