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Palladium-Catalyzed Reactions of Indolic Triflate with Allylic Alcohols

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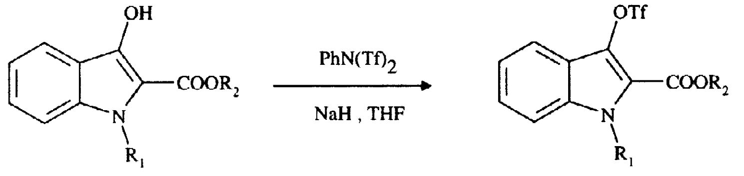
Abstract : Reactions of 3-indolic triflate **2a** with allylic alcohols in presence of palladium (II) acetate gave access to aldehydic compounds and in a more surprising way to *C*-2 substituted products and oxindole derivatives. © 1997 Elsevier Science Ltd. All rights reserved.

Palladium-catalyzed reactions of aryl halides or triflates with allyl or homoallyl alcohols lead to the formation of β or γ-aromatic aldehydes or ketones, which is the usual pathway.[1-4] The formation of the carbonyl compounds presumably proceeds *via* palladium-complexed enols.[5,6] The selective formation of the substituted allylic alcohols was rationalized by assuming a four-membered intermediate, where the hydrogen atom (Hα) on the hydroxyl-bearing carbon is located unfavorably toward a *syn* palladium hydride elimination.[7] Recently Kang[8] *et al.* reported the exclusive arylation of allylic alcohols with hypervalent aryl iodonium salt and pointed out the role of the base in the key step of β-hydride elimination for regenerating the Pd(0) species. In contrast to the formation of carbonyl group, the palladium-catalyzed arylation of *N*-alkyl *O*-allyl carbamates afforded only the cinnamyl alcohol.[9] Due to a coordination of the nitrogen atom on the Pd(II) intermediate, the Hα-Pd elimination was not favored.

In this letter we report our preliminary results in the palladium-catalyzed reaction of allylic alcohols with functionnalized 3-indolic triflates **2** which are easily accessible from the corresponding hydroxyesters **1** and N-phenyltriflimide (Scheme 1).[10,11]

Scheme 1



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2a R$_1$= H R$_2$= CH$_3$ 87%
2b R$_1$= CH$_3$ R$_2$= C$_2$H$_5$ 90%

Recently, a domino Heck-aldol condensation of 2-bromobenzaldehyde with allylic alcohols has been described by Dyker *et al.*[12] The reaction of triflate **2b** with allylic alcohols in presence of palladium acetate is highly dependent on the experimental conditions, as listed in Table[14] In fact, four different products have been isolated: the 2-allyloxy ester and 2-homoallyloxy ester **3**, the ethyl 3-hydroxy-2-oxo-3-indolinecarboxylate **4**[13] or the aldehydic compounds **5** and **6**

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(Scheme 2). All reactions were carried out at 100°C in DMF, excepted for entries 2 and 4 (CH_3CN), in presence of 2 equivalents of base.

Scheme 2

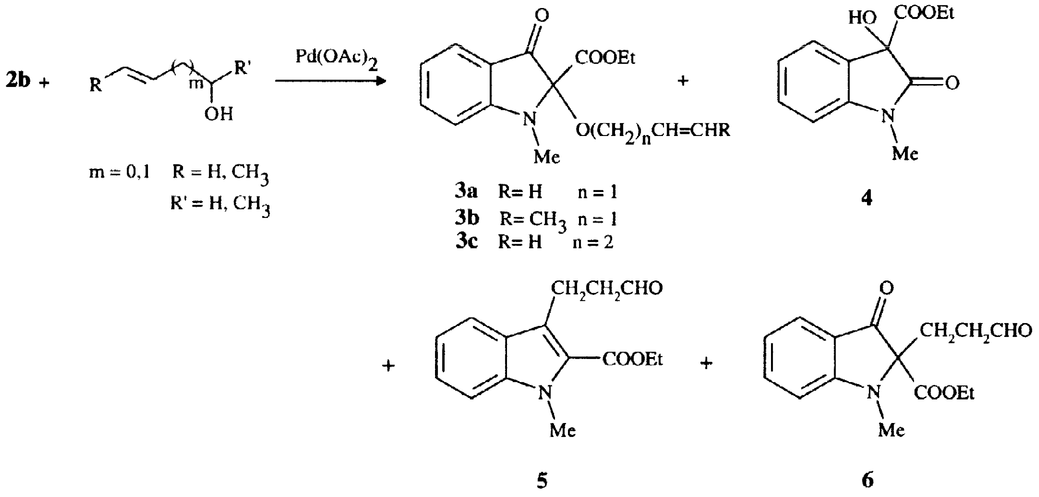


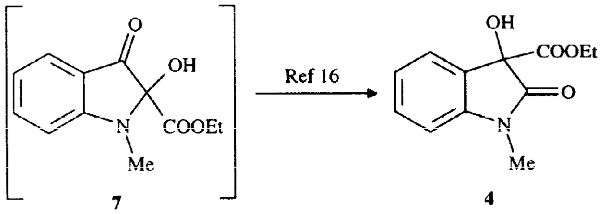
Table. Reactions of Allylic Alcohols with Triflate **2b**

Entry	m	R	R'	$Pd(OAc)_2$ (eq.)	PPh_3 (eq.)	Base (2eq.)	Reaction Time	n	3	4	5	6
										Yield (%)		
1	0	H	H	0.06	0.03	Et_3N	5h	1	45	13	-	-
2*	0	H	H	0.06	0.03	Et_3N	12h	1	57	-	-	-
3	0	H	H	0.2	0.1	Et_3N	3h	1	17	20	-	-
4*	0	H	H	0.06	-	K_2CO_3	4h	1	41	-	-	-
5	0	H	H	0.02	-	$NaHCO_3$	4h	1	-	-	-	43
6	0	H	H	0.1	-	$NaHCO_3$	4h	1	-	21	18	18
7	0	H	CH_3	0.06	0.03	Et_3N	1h	1	-	53	-	-
8	0	H	CH_3	0.02	-	$NaHCO_3$	2h	1	-	40	-	-
9	0	CH_3	H	0.06	0.03	Et_3N	24h	1	25	-	-	-
10	1	H	H	0.06	0.03	Et_3N	6h	2	19	-	-	-
11	1	H	H	0.02	-	$NaHCO_3$	5h	2	16	7	-	-

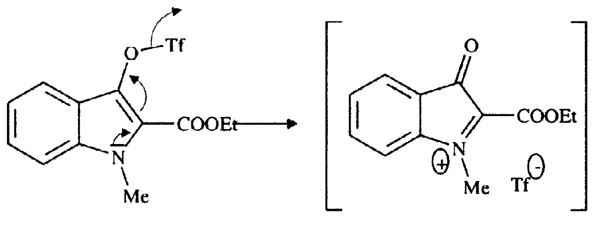
*Solvent used : acetonitrile

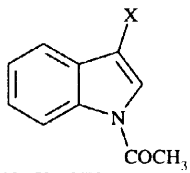
Thus reaction of the triflate **2b** with allyl alcohol in presence of catalytic palladium acetate (0.06 equiv.), triphenylphophine as ligand (0.03 equiv.) and trietylamine as base (2 equiv.), afforded a mixture of the allyloxyketoester **3a** and compound **4** in 45% and 13% yields respectively (entry 1).[15] Using acetonitrile instead of dimethylformamide, as solvent, gave exclusively the 2-allyloxy compound **3a** (entry 2). A mixture of compounds **3a** and **4** (entry 3) is still obtained by increasing the amount of $Pd(OAc)_2$. The 3-hydroxy compound **4**[13] can result from the *in situ* rearrangement of 2-hydroxy compound **7**,[16] which itself could be obtained from a nucleophilic attack of water (as traces) and/or from the corresponding acetate (Scheme 3).

Scheme 3



The use of K_2CO_3 instead of an organic base (entry 4) afforded only compound 3a. Attack on the indolic *C*-2 atom by nucleophilic reagents has been recently described[17] on pyrrolo[1,2-*a*]indolic triflate. The mechanism **involved the formation of an acyl iminium salt (after loss of the triflinate ion) as depicted below.** This process is facilitated by donation of the lone pair from nitrogen atom and the stabilizing effect of a polar aprotic solvent. In our case, the nucleophilic attack of the allyl alcohol on the *C*-2 atom is exclusive at the expense of the Heck reaction (entries 1-4).

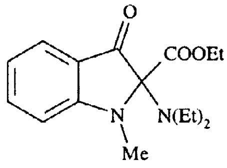




10 X= OTf
11 X= CH=CHCH$_2$OH

The formation of **3a** was also observed in absence of $Pd(OAc)_2$, but with a longer reaction time and a lower yield. To obtain a product corresponding to a standard Heck reaction, we have carried on several different experimental conditions. The use of an inorganic base such as $NaHCO_3$ and 0.1 equiv. of $Pd(OAc)_2$, provided the aldehyde **5** accompanied with hydroxy compound **4** and *C*-2 alkylated compound **6** (entry 6). If only 0.02 equiv. of $Pd(OAc)_2$ was used, no Heck product was isolated[18] (entry 5), but we obtained only compound **6** in 43% yield.[19]

The hydroxy compound **4** is exclusively obtained from 1-buten-3-ol (entries 7,8). In the case of but-2-en-1-ol (entry 9) and but-1-en-4-ol (entries 10,11) yields of compounds **3b**, **3c** and **4** were low. Indeed, when the reaction was carried out with triethylamine, product **8** was isolated (20% yield). Compounds **8** and **9** were obtained respectively in 26 and 24% yield when the triflate **2b** was heated in DMF with triethylamine in the absence of allylic alcohols. The reactivity of DMF, recently reported in palladium-catalyzed reactions[20] may explain the formation of **9**.



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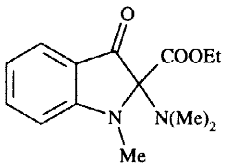

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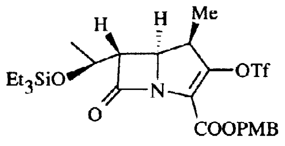

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It is noteworthy the importance of the ester group on the indolic *C*-2 position. The Heck reaction of the indolic triflate **10** with allyl alcohol afforded the "normal" Heck product **11** using conditions of entry 1. This normal behavior was also reported by Gribble *et al.* for similar reactions.[9] The presence of the ethyl ester group in 2-position modifies the reactivity of the 3-indolic triflate and this is due to the indolic structure since carbapenem-2-yl triflate **12** has an usual reactivity towards allyl alcohol.[21]

Reactions with the « free » NH indolic triflate **2a** were unproductive and afforded degradation of the starting material.

We have reported here the possibility of introducing a nucleophilic species (allylic alcohol or amine) in the 2-position of indole. Such compounds are not accessible directly from hydroxyester **1b** which only reacted with electrophiles. The reactivity of 1,2-diamines towards **2b** is currently investigated, in order to obtain cyclic compounds like quinoxaline, as potential DNA intercalating agents.

References and Notes :

1- Melpolder, J.B.; Heck, R.F. *J. Org. Chem.* **1976**, *41*, 265-272.

2- Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2-7.

3- Tamaru, Y.; Yamada, Y.; Yoshida, Y. *Tetrahedron* **1979**, *35*, 329-340.

4- De Meijere, A.; Meyer, F.E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379-2411.

5- Kao, L-C.; Stakem, F.G.; Patel, B.A.; Heck, R.F. *J. Org. Chem.* **1982**, *47*, 1267-1277.

6- Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1991**, 324-325.

7- Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133-1136.

8- Kang, S-K.; Lee, H-W.; Jang, S-B.; Kim, T-H.; Pyun, S-J. *J. Org. Chem.* **1996**, *61*, 2604-2605.

9- Ono, K.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1994**, *35*, 4133-4136.

10- Gribble, G.W.; Conway, S.C. *Synth. Comm.* **1992**, *22*, 2129-2141.

11- Joseph, B.; Malapel, B.; Mérour, J.-Y. *Synth. Comm.* **1996**, *26*, 3289-3295.

12- Dyker, G.; Grundt, P. *Tetrahedron Lett.* **1996**, *37*, 619-622.

13- Guyot, A.; Martinet, J. *C.R. Acad. Sci.*, **1913**, *156*, 1625-1628. An authentic sample of compound **4** has been prepared according this reference.

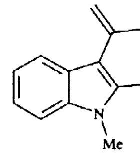
14- Typical procedure reaction between the indolic triflate **2b** and allylic alcohol: To $Pd(OAc)_2$ (10 mg, $4.45.10^{-2}$ mmol) and PPh_3 (6mg, $2.28.10^{-2}$mmol) was added under argon a solution of the triflate **2b** (200 mg, 0.57 mmol), the allylic alcohol (3 equiv.) and the base (2 equiv.) in DMF (10 ml). The solution was stirred at 100°C and the reaction was monitored by TLC. When all the starting material has disappeared, H_2O (20 ml) was added and the aqueous layer was neutralized with a 10% HCl solution and twice extracted with ethyl acetate (2x10 ml). The organic layers were washed with water, brine and dried ($MgSO_4$). After filtration and evaporation the residue was purified on a silica gel column using ethyl acetate/petroleum ether (2:8 v/v) as eluent.

3a : yellow oil; IR (film) : ν=1760, 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) : δ=1.14 (t, 3H, **CH_3**, J=7.3Hz); 2.85 (s, 3H, **NMe**); 3.78-3.92 (m, 2H, **OCH_2**); 4.10-4.19 (m, 2H, OCH_2CH_3); 5.05-5.19 (m, 2H, $CH=CH_2$); 5.79-5.92 (m, 1H, **CH=**); 6.69-6.76 (m, 2H, **Har**); 7.43-7.49 (m, 2H, **Har**); ^{13}C NMR($CDCl_3$) δ=14.1 (**CH_3**); 28.0 (**CH_3**); 62.4 (**CH_2**); 65.6 (**CH_2**); 95.3 (**C-2**); 108.6 (**CH=**); 117.9 (**C**); 118.1 (**CH**) 118.8 (**$=CH_2$**); 118.9 (**C**); 125.1 (**CH**); 113.4 (**CH**); 138.6 (**CH**); 161.1 (**C**); 165.1 (**CO**); 194.7 (**CO**); SM (M^++1)=276.

4 : mp=138-140°C (litt.[13] mp=130°C); IR (KBr) : ν=3302, 1756, 1708 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) : δ=1.10 (t, 3H, **CH_3**, J=7.35 Hz); 3.18 (s, 3H, **NMe**); 4.10-4.20 (m, 3H, **OCH_2CH_3**, **OH**); 6.81 (d, 1H, **Har**, J=8.1 Hz); 7.03 (t, 1H, **Har**, J=7.3 Hz); 7.21 (d, 1H, **Har**,, J=8.1 Hz); 7.32 (t, 1H, **Har**, J=7.3 Hz); ^{13}C NMR (62.90 MHz, DMSO) : δ=15.2 (**CH_3**); 27.5 (**CH_3**); 62.7 (**CH_2**); 78.6 (**C-3**); 110.5 (**CH**); 124.1 (**CH**); 124.8 (**CH**); 129.7 (**C**); 131.7 (**CH**); 145.5 (**C**); 170.4 (**CO**); 174.4 (**CO**); SM : (M^++1)=236; (M^++18)=253.

5 : yellow oil; IR (film) : ν=1742, 1705cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) : δ=1.46 (t, 3H, **CH_3**, J=7.0 Hz); 2.83 (t, 2H, **CH_2**, J=7.3 Hz); 3.43 (t, 2H, **CH_2**, J=7.3 Hz); 4.03 (s, 3H, **NMe**); 4.42 (q, 2H, **OCH_2**, J=7.3 Hz); 7.04-7.12 (m, 1H, **Har**); 7.29-7.33 (m, 1H, **Har**); 7.68-7.72 (d, 2H, **Har**, J=8Hz); 9.88 (s, 1H, **CHO**); ^{13}C NMR ($CDCl_3$): δ= 13.3 (**CH_3**); 17.2 (**CH_2**); 31.1 (**CH_3**); 44.1 (**CH_2**); 59.6 (**CH_2**); 109.2 (**CH**); 119.1 (**CH**); 119.3 (**CH**); 121.8 (**C**); 123.8 (**C**); 124.4 (**CH**); 125.1 (**C**); 137.6 (**C**); 161.4 (**CO**); 201.2 (**CHO**); SM : (M^++1)=260.

15- In some cases we obtained in an erratic manner the formation of a lactonic compound as the result of an Heck reaction by a different regioselectivity.

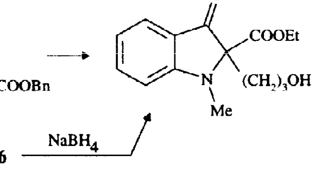


16- Kershaw, J.W.; Taylor, A. *J. Chem. Soc.* **1964**, 4320-4323.

17- Edstrom, E.D.; Yu, T. *J. Org. Chem.* **1995**, *60*, 5382-5383.

18- Triflate **2b** reacted on the 3-position in Suzuki or Stille reactions but also with propargylic alcohol (following entry 1) to give respectively the desired products in excellent yield (80-90%)(unpublished results).

19- An intermediate palladium enolate, in 3-position, could explain the formation of **6**. The structure of **6** has been confirmed by a C-2 alkylation of **1b** with benzyl 3-bromopropanoate, followed by hydrogenolysis of the benzyl ester, reduction of the acid function ($BH_3.Me_2S$) gave the desired alcohol. An other way to this alcohol was achieved by reduction of compound **6**.



20- Toffano, M.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1997**, *38*, 77-80.

21- Nishi, K.; Narukawa, Y.; Onoue, H. *Tetrahedron Lett.* **1996**, *37*, 2987-2988.