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Palladium (II) Catalysed Claisen Rearrangement: Synthesis of Inaccessible N-allyl-2(1H)-pyridones from 2-(allyloxy)pyridines+

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Abstract: *6-Aryl-4-trifluoromethyl-2(1H)-pyridones (1) yielded O-allylated products (3) exclusively on allylation. The inaccessible N-allylated products (4) were synthesised in good yields from the O-allylated products by utilising Pd(II) catalysed [3,3] sigmatropic rearrangement.* Copyright © 1996 Elsevier Science Ltd

Substituted N-alkyl-2(1H)-pyridones are common features of many biologically active substances[1]. Since activity is primarily dependent on lipophilicity, the introduction of a trifluoromethyl group enhances not only the potency but also the duration of action[2]. Accordingly, we wanted to prepare N-alkylated/allylated products of **1** which were prepared by the Seymour procedure[3]. But our study[4] reveals that a trifluoromethyl group at C-4 or C-6 in the pyridin-2-one ring directs the exclusive formation of O-alkylated/allylated products of type **3** and no N-alkylated/allylated ones are formed, irrespective of the nature of the alkylating agent whether it is α-haloester, α-haloamide, halo acetonitrile or substituted allyl halide. Such a regioselectivity has been shown to be due to the role of the powerful electron withdrawing trifluoromethyl group in inducing an electronic delocalisation property in the ring causing enhanced charge density on the oxygen atom. Having obtained O-allylated products **3** from **1** on allylation, we attempted Claisen [3,3] sigmatropic thermal rearrangement of **3** into **4** at 200°C for 8 hours to obtain the N-allylated pyridones but no product was formed, presumably due to the stability conferred by the trifluoromethyl group on **3**.

Reviewing the metal-catalysed Claisen rearrangements that are usually much faster than thermal reactions, we selected palladium (II) catalyst. Following the reports on the use of Pd(II) complexes in bringing about [3,3] sigmatropic rearrangements in 1,5 dienes[5], allyl esters[6], allyl imidates[7]

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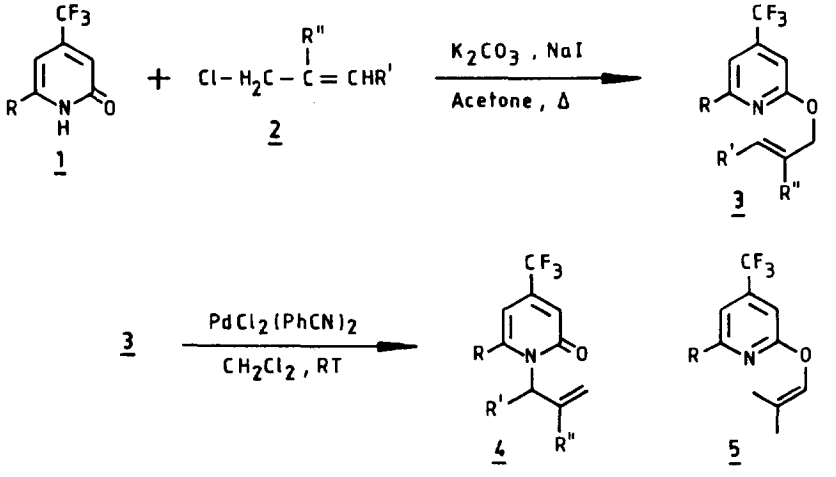
and allyl vinyl ethers[8,9], we report here for the first time that 2-allyloxy-6-aryl-4-trifluoromethyl pyridines (3) gave exclusively the required Claisen products, N-allyl-6-aryl-4-trifluoromethyl-2(1H)-pyridones (4) with dichlorobis(benzonitrile)palladium (II) catalyst, $[PdCl_2(PhCN)_2]$[10]. The highly regioselective N-allylation rearrangement to the exclusion of C-3 allyl product shows that the allyl imidate system in 3 is far more reactive than the allyl vinyl ether system.



Treatment of **1** with substituted allyl chlorides (2) (1:1 equivalent) in dry acetone, potassium carbonate and sodium iodide under reflux for 5 hours, led to the exclusive formation of 2-allyloxy pyridines (3).

When the 2-allyloxy pyridines (3) and $[PdCl_2(PhCN)_2]$ (0.1 equivalent) were stirred in dry dichloromethane under nitrogen at room temperature for 1 to 7 hours (monitored by TLC), it resulted in the formation of **4** exclusively, which were isolated by column chromatography. Representative spectroscopic data for **3** and **4** are given in reference 11. However, the 2-allyloxy compound **3** ($R=C_6H_5$, $R'=C_6H_5$, $R''=H$) did not undergo rearrangement, even on increasing the catalyst concentration, temperature and time, presumably due to electronic and steric factors. Also, the 2-allyloxy compound **3** where $R''=CH_3$ gave **5** in which the double bond underwent isomerisation. This observation (entries 4,9,13,17) is in tune with the "cyclization-induced rearrangement" pathway[5,6]. A methyl group at the olefinic 2-position in allylic imidates is known to cause inhibition of reactivity[8] by preventing the formation of carbon-palladium bond in the cyclization stage. Here also in compounds **3** where $R''=CH_3$, the same inhibition of rearrangement takes place, but the product isolated is the double bond isomerised product **5**.

Table 1 summarises the results on allylation as well as rearrangement.

Table 1: Products **3**, the 2-allyloxy pyridines and **4**, the N-allyl-2(1H)-pyridones

Entry	R	R'	R"	Yield of 3(%)[a]	Yield of 4(%)[a]
1	C_6H_5	H	H	97	100
2	C_6H_5	CH_3	H	93[b]	96
3	C_6H_5	C_2H_5	H	95	93
4	C_6H_5	H	CH_3	89	90[c]
5	C_6H_5	C_6H_5	H	93	NR
6	p-$CH_3C_6H_4$	H	H	98	100
7	p-$CH_3C_6H_4$	CH_3	H	96[b]	90
8	p-$CH_3C_6H_4$	C_2H_5	H	90	96
9	p-$CH_3C_6H_4$	H	CH_3	92	93[c]
10	p-ClC_6H_4	H	H	94	100
11	p-ClC_6H_4	CH_3	H	90[b]	88
12	p-ClC_6H_4	C_2H_5	H	96	94
13	p-ClC_6H_4	H	CH_3	94	90[c]
14	C_2H_5	H	H	88	100
15	C_2H_5	CH_3	H	86[b]	84
16	C_2H_5	C_2H_5	H	84	93
17	C_2H_5	H	CH_3	80	91[c]

[a] Yields refer to analytically pure products isolated by column chromatography. [b]Contains mixture of cis and trans in 1:2 ratio. [c]Product (**5**). NR: No reaction.

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11. Typical spectroscopic data for compound **3** ($R=C_6H_5$, $R'=C_2H_5$, $R''=H$): IR: 1240, 1585 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ1.02(t,J=9Hz,3H,CH_3), 2.10(quintet,J=9Hz,2H,CH_2), 4.90(d,J=9.4 Hz,2H,OCH_2), 5.70-5.90(m,2H,-CH=CH-), 6.87(s,1H,H-C(3)), 7.32-7.48(m,4H,three phenyl Hs and H-C(5)), 8.00(m,2H,two phenyl Hs) ppm; Mass (m/z) 307 (M^+), 306, 278, 239, 211, 68. For compound **4** ($R=C_6H_5$, $R'=C_2H_5$, $R''=H$): IR:1260, 1685 (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 0.61 (t,J=9Hz 3H,CH_3), 1.90(m,J=9,8.5Hz,2H,CH_2), 4.22(q,J=8.5,8Hz,1H,N-CH), 4.80(d,J=18Hz, 1H,trans =CH), 5.04(d,J=10Hz,1H,cis =CH), 6.00(s,1H,H-C(3)), 6.29-6.50(m,J=18,10,8.5Hz, 1H,-HC=), 6.69(s,1H,H-C(5)), 7.26 (m,2H,phenyl Hs, 7.41(m,3H,phenyl Hs) ppm; ^{13}C NMR (200 MHz,$CDCl_3$): δ 161.7(CO),152.3(C(4)),139.6(CF_3),136.2(C(3)),135.5(C(6)),129.7(C(4')), 128.5(C(2', 3',5')), 118.5(C(1',6')), 117.5(C(5)), 102.6(=CH), 96.2(=CH_2), 66.3(N-CH), 24.6(CH_2), 11.1(CH_3) ppm; Mass(m/z) 307(M^+), 278, 239, 211, 68.

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