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SYNTHESIS OF α-AMINOACIDS BY CATALYTIC PALLADIUM (0) ALKYLATION OF SCHIFF BASES

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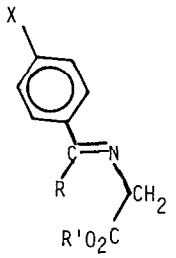
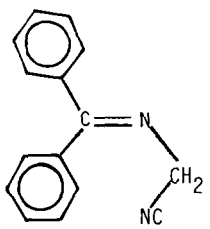
Abstract : Schiff bases 1 b, 1 c, 2 derived from glycine ester or aminoacetonitrile were alkylated with allylic acetates 3 a, 3 b or allylic carbonates 3 c, 3 d, 4 a, 4 b (under neutral conditions) in the presence of catalytic amount of palladium (0). After hydrolysis higher and functionalized α-aminoesters were obtained in good yields (50 to 85 %).

Since the first report of STORK et al (1) on the alkylation of the anion of Schiff base 1 a derived from glycine ester, efficient and elegant routes to α-aminoacids have been widely developped. Schiff bases can be alkylated in the presence of strong bases (2) and under various phase transfer conditions (3).



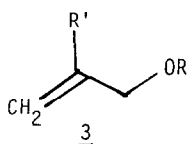
1



2

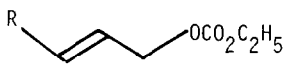
a : R=X=H ; R'=C_2H_5
b : R=H ; X=Cl ; R'=C_2H_5
c : R=Ph ; X=H ; R'=CH_3

As part of our program on the α-aminoacids synthesis we investigated very recently the palladium catalyzed alkylation of nitroacetic esters (4,5) and Schiff bases derived from α-aminoesters. We wish to report here a convenient approach for the synthesis of higher and functionalized α-aminoacids by palladium (0) alkylation of Schiff bases (6) with various allylic derivatives 3, 4 ; (Table I).



3

a : R'=H ; R=$COCH_3$
b : R'=CH_3 ; R=$COCH_3$
c : R'=H ; R=$CO_2C_2H_5$
d : R'=CH_3 ; R=$CO_2C_2H_5$

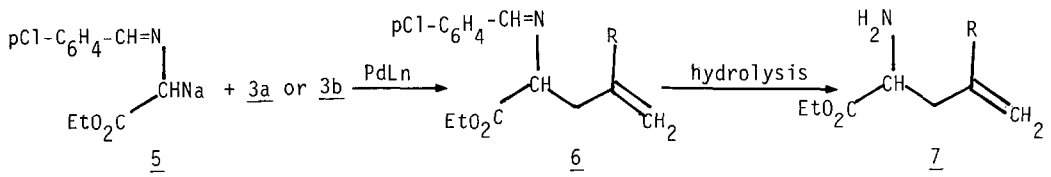


4

a : R=Ph
b : R=CH_2OAc

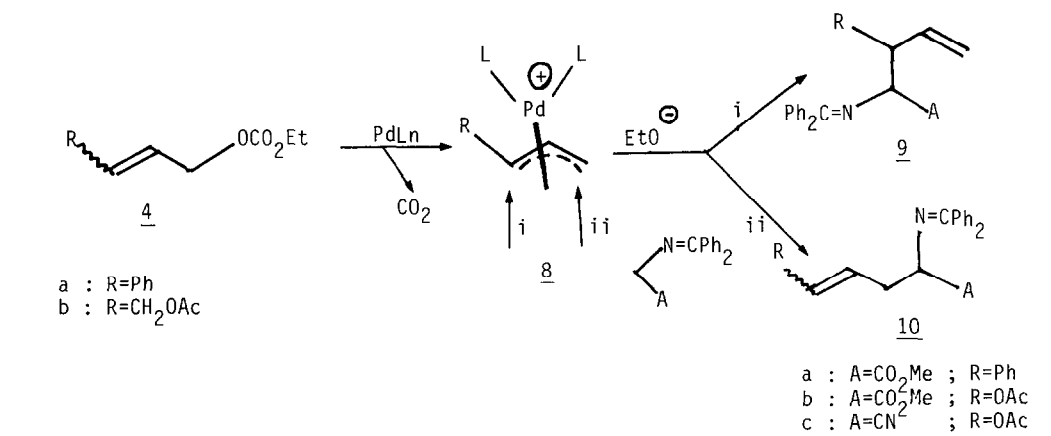
Schiff bases of glycine ester or aminoacetonitrile derived from aromatic aldehydes or ketones (e.g. p-chlorobenzaldehyde and benzophenone) have been chosen because they are cristalline starting materials readily available (7) instead of Schiff base 1 a obtained from benzaldehyde which is a less stable oil.

The catalytic classical palladium-alkylation of 1 b, with allylic acetates 3 a, 3 b, was carried out with the preformed anion of Schiff base (from NaH in THF) and gave after hydrolysis and extractive work up higher monoalkylated α-aminoesters 7 in 50-65 % yield (runs 1,2).



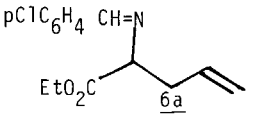
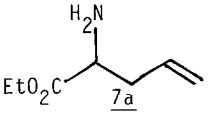
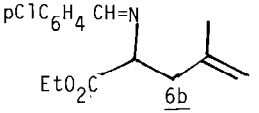
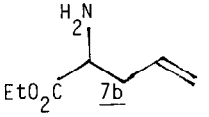
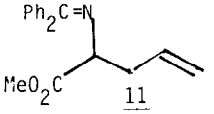
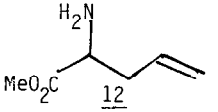
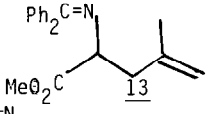
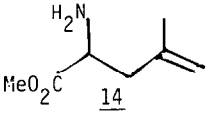
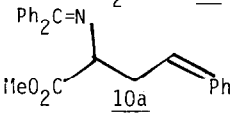
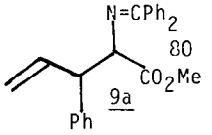
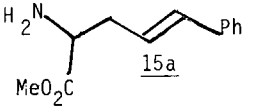
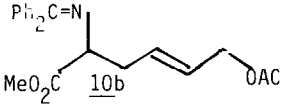
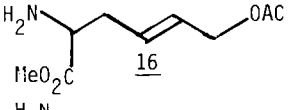
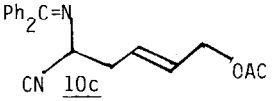
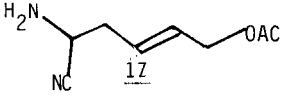
More interestingly the palladium-catalyzed alkylation can be performed *under neutral conditions* starting from allylcarbonates 3c, 3d, 4a,b (8). This alkylation without preformation of the anion of Schiff bases gave only monoalkylated products 6b,11,13 and after hydrolysis the α-aminoesters 7b, 12, 14, in good yield (70-90%) (runs 3,4,5) (Table I).

The regioselectivity of the alkylation of 1c and 2 was tested with carbonate of cinnamyl alcohol 4a and with the bis allylic - 1,4 acetate carbonate 4b.



The reaction of 4a occurs in good yield (80%) almost completely at the less substituted end(path ii) of η^3 palladium complex 8 with formation of 9a and 10a (9) in a ratio 1/19 (run 6). In contrast, alkylation of 4b was completely regioselective and we obtained monofunctionnalized alkylated 10b, 10c products (10) in good yields (70-80%) (runs 7,8) (Table I).

TABLE I

Run	*Schiff base*	*Allylic substrate*	*Conditions*[a] *t(h)*	*T°C*	*Products*	*(yield %)*	*Aminoester*[b]	*(yield %)*
1	1b	3a	1	20	 6a	70	 7a	50
2	1b	3b	1	20	 6b	60	 7b	65
3	1b	3d	1	20	6b	70	7b	65
4	1c	3c	2	20	 11	80	 12	75
5	1c	3d	2	20	 13	90	 14	85
6	1c	4a	8	20	 10a  9a	80	 15a	70
7	1c	4b	8	20	 10b	70	 16	75
8	2	4b	8	20	 10c	80	 17	70

a) *General Procedure with allylic carbonates 3c,d,4a,b.*
Under argon to a stirred solution of Schiff base 1b,c or 2 (2mmoles) and allyl carbonate 3c,d or 4a,b (2mmoles) in 2ml of dry THF was added 0,025 to 0,05 mmol of Pd(dppe)$_2$. The mixture was allowed at room temperature for a period of extended time. The solvent was evaporated, the crude material was poured into 20ml of ether and then filtered through a pad of Celite. After removal of solvent, the mixture was chromatographed on silica gel to give pure alkylated Schiff bases.

b) *After hydrolysis with HCl (10%) at room temperature for 10mn and classical work up.*

The palladium catalyzed alkylation under neutral conditions provides a particulary attractive approach for the preparation of β,γ-unsaturated α-aminoacids derivatives and natural α-aminoacids with interesting biological properties. For example, in this paper we synthesized the methyl ester of trans-2, amino-5, phenyl-4, pentenoic acid 15a inhibitor of S-adenosyl transferase (11) (under its acid form) ; allyl glycine methyl ester and leucine methyl ester (12) were also prepared (13).

The applicability of this process to asymmetric synthesis is under investigation.

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7) M.J.O'Donnell and R.L.Polt, J.Org.Chem. 47, 2663 (1982).

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9) The two regioisomers were purified by flash chromatography over alumina, eluent : 10 % Ethyl acetate in Hexane.
10a : IR (film) 3030, 2950, 1730, 1620, 1435, 1250, 1170, 970 cm^{-1}. RMN ^1H 80 MHz $CDCl_3$: 7.75-6.95 (m 15H) ; 6.5-5.8 (m 2H) ; 4.20 (t 1H) ; 3.75 (s 3H) ; 2.82 (m 2H).
9a : IR (film) 3030, 3020, 2910, 1730, 1620, 1595, 1570, 1440, 1310, 960 cm^{-1}.
RMN (80 MHz, $CDCl_3$) 8-7.15 (m 15H) ; 6.75-6 (m 1H) ; 5.45-5.12 (m 2H) ; 4.25 (t 1H) ; 4.12 (m 1H) ; 3.75 (s 3H).

10) 10c : IR (film) 3020, 2950, 2230, 1730, 1610, 1440, 1360, 1290, 1230, 1020, 960. RMN 80 MHz $CDCl_3$: 7.87-7.15 (m 10H) ; 5.75 (m 2H) ; 4.5 (m 2H) ; 4.3 (t 1H) ; 2.67 (m 2H); 2.02 (s 3H).
10b : RMN (60MHz, $CDCl_3$) : 7.75-6.95 (m 10H) ; 5.50 (m 2H) ; 4.42 (m 2H) ; 4.10 (t 1H) 3.75 (s 3H) ; 2.6 (m 2H) ; 2.00 (s 3H).
IR (film) 2950, 2920, 1720, 1590, 1450, 1365, 1230, 1010, 960.

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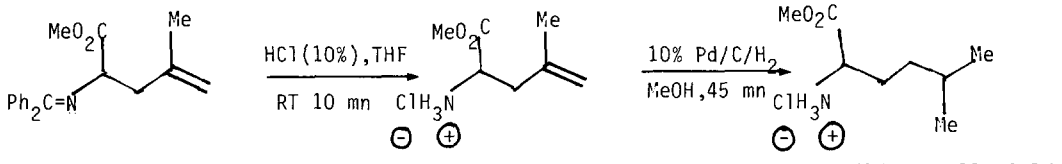
12)



70% overall yield from 1c

13) We wish to thank Centre National de la Recherche Scientifique (CNRS) for financial support : D.F.thanks DGRST for Grant (1983-1985).

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