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Synthesis of Vinca Alkaloids and Related Compounds. 8.[1] Unusual Alkylation of an Enamine

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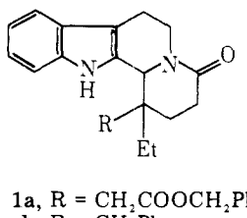
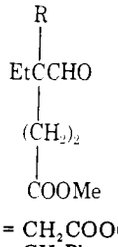
As a promising intermediate for the synthesis of indoloquinolizidine derivative **1a**, we intended to prepare the aldehyde's diester **2a** through the alkylation of enamine **3**[2] with benzyl α-bromoacetate **4**. The alkylation of enamines by α-halocarbonyl compounds is known to proceed smoothly.[2,3]

Enamine **3** was prepared from aldehyde **2c**[4] and reacted with benzyl α-bromoacetate. The aldehyde obtained from the hydrolysis was treated with tryptamine and surprisingly the indole lactam (**1b**) was obtained instead of the expected **1a.**

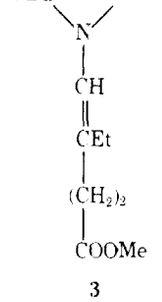
To fully substantiate the structural assignment for **1b**, enamine **3** was alkylated with benzyl chloride. Aldehyde **2b** obtained after hydrolysis was treated with tryptamine to generate a crystalline material identical with **1b.**



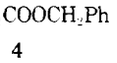
1a, R = CH_2COOCH_2Ph
b, R = CH_2Ph



2a, R = CH_2COOCH_2Ph
b, R = CH_2Ph
c, R = H



3



4

Although it is well known that esters of strong acids, e.g., those of *p*-toluenesulfonic acid, have strong alkylating power,[5] the fact that **4** alkylates with its benzyl group instead of the very reactive carbon atom α to the carbonyl function seems to be rather surprising and represents a small contribution to the scope and limitations of enamine chemistry.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded using a SPEKTROMOM 2000 instrument; NMR spectra were obtained with Perkin-Elmer R-12 spectrometer. Mass spectra were taken with a AEI-MS-902 spectrometer system.

Methyl (5-Dibutylamino)-4-ethyl-4-pentenoate (3). A solution of methyl 4-formylhexanoate[4] (**2c**, 50.0 g, 316 mmol) and dibutylamine (46.0 g, 365 mmol) in dry benzene (100 mL) was refluxed for 2 h under a water separator meanwhile 5.5 mL (96.6%) of water was distilled off from the system. After evaporating the solvent under reduced pressure the residue was distilled to give **3** as a yellow oil (61.8 g, 72.6 %): bp 108–110 °C (0.2 mm); $n^{25}D$ 1.4532; IR (film) 1747 (>C=O), 1660 cm^{-1} (>C=C<); NMR (CCl_4) δ 3.49 (s, 3, CH_3O), 5.12 (s, 1, -CH=C<).

Methyl (4-Benzyl-4-formyl)hexanoate (2b). (a) A solution of dibutylamine (12.9 g, 100 mmol) and methyl 4-formylhexanoate (**2c**, 15.8 g, 100 mmol) in dry benzene (60 mL) was refluxed for 8 h under a water separator meanwhile 0.9 mL (50.0%) of water was distilled off from the mixture. Bromacetic acid benzyl ester (**4**, 22.9 g, 100 mmol) and dry acetonitrile (20 mL) were added and the mixture was refluxed for 5 days (~120 h). Glacial acetic acid (6 mL) and water (18 mL) were added and the heating was continued for 1 h. The solution was cooled to room temperature and diluted with water (300 mL) and the product was extracted with ether. After washing with water, 5% sodium hydrogen carbonate solution, and water, the ether was dried and evaporated under reduced pressure. Distillation of the residue afforded **2b** as a yellow oil (6.4 g, 25.7%): bp 126–128 °C (0.2 mm); $n^{26}D$ 1.5070; IR (film) 1740 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 0.86 (t, 3, CH_3CH_2), 2.82 (s, 2, benzyl CH_2), 3.63 (s, 3, CH_3O), 7.56–6.86 (m, 5, ArH), 9.60 (s, 1, aldehyde H); MS 248 (12.5), 220 (29.9), 234 (10.5), 188 (72.1), 142 (57.4), 129 (55.4), 117 (30.5), 105 (27.7), 91 (*100*).

(b) A solution of methyl 4-formylhexanoate (**2c**, 38.0 g, 240 mmol) and dibutylamine (31.0 g, 240 mmol) in dry benzene (130 mL) was refluxed for 8 h under a water separator meanwhile 2.2 mL (50.9%) of water was distilled off from the system. The benzene was removed in reduced pressure and the residue was dissolved in dry dioxane (120 mL). Benzyl chloride (45.7 g, 360 mmol) was added and the mixture was refluxed for 5 days (~120 h). After adding glacial acetic acid (14.4 mL) and water (43.2 mL) the heating was continued for 2 h. The solution was cooled to room temperature, diluted with water (600 mL), and extracted with ether. After washing with water, 5% sodium hydrogen carbonate solution, and water the ether was dried and removed under reduced pressure. The residue was distilled in vacuo to give **2b** as a yellow oil (7.0 g, 11.7%): bp 123–125 °C (0.15 mm); $n^{27}D$ 1.4990.

The product is identical in every respect with that obtained by the method "a".

1-Benzyl-1-ethyl-1,2,3,4,5,6,7,12-octahydro-12b*H*-indolo[2,3-*a*]quinolizin-4-one (1b). (a) A solution of tryptamine (0.5 g, 3.13 mmol) and methyl (4-benzyl-4-formyl)hexanoate (**2b**, prepared by method "a") (1.5 g, 6.04 mmol) in glacial acetic acid (5 mL) was refluxed for 72 h. After 27 h of heating a further amount (0.5 g, 2.01 mmol) of **2b** was added. The solution was diluted with water (50 mL), stirred, cooled (ice bath), and alkalized with 40% aqueous sodium hydroxide. The product was extracted with methylene chloride, the extract was dried, and the solvent was removed under reduced pressure. The residue was triturated with petroleum ether. Crystallization of the crude product from ethyl acetate afforded white, crystalline **1b** (0.35 g, 31.2%), mp 210–212 °C. Recrystallization from ethyl acetate raised the mp to 212–213 °C. Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.40; H, 7.31; N, 7.81. Found: C, 80.35; H, 7.18; N, 8.02. IR (KBr) 3335 (indole NH), 1605 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 4.86 (s, 2, benzyl CH_2), 7.68–6.80 (m, 9, ArH), 7.96 (s, 1, indole H); MS 358 (70), 329 (0.4), 267 (7.3), 266 (9.9), 251 (4.4), 211 (30), 170 (*100*), 169 (61).

(b) A solution of tryptamine (1.0 g, 6.24 mmol) and methyl (4-benzyl-4-formyl)hexanoate (**2b**, prepared by method "b") (1.85 g, 7.45 mmol) in glacial acetic acid (10 mL) was reacted and worked up as in "a", to give white, crystalline **1b** (0.6 g, 26.8%), mp 212–213 °C.

The product was identical in every respect with that obtained by method "a".

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Registry No.—**1b**, 67938-50-5; **2b**, 67938-51-6; **2c**, 40630-06-6; **3**, 67938-52-7; **4**, 5437-45-6; dibutylamine, 111-92-2; benzyl chloride, 100-44-7; tryptamine, 61-54-1.

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Palladium-Catalyzed Arylation of Conjugated Dienes

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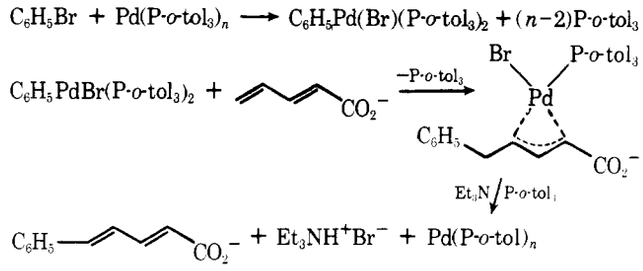
The palladium-catalyzed arylation of simple olefins with aryl halides is a versatile and convenient method for the synthesis of arylated olefins.[1] Similar reactions with conjugated dienes would be expected to produce arylated dienes. Some differences and perhaps complications could be expected, however, since π-allylic palladium species probably would be intermediates in the reaction.[2] We now report a study of this reaction.

Results and Discussion

It was anticipated from previous results[3] that aryl halides and dienes conjugated with carbonyl groups would react under our usual conditions catalytically to produce arylated dienes. This proved to be the case with (*E*)-2,4-pentadienoic acid. Bromobenzene and the pentadienoic acid reacted with 1 mol % of palladium acetate, 2 mol % of tri-*o*-tolylphosphine, and 2 equiv of triethylamine at 100 °C in 20 h to form (*E,E*)-5-phenyl-2,4-pentadienoic acid in 92% (isolated) yield. We believe that a π-allylic palladium(II) intermediate is involved which readily undergoes elimination of the palladium hydride group because of the activating influence of the neighboring carboxylic acid (anion) group. 3,4-Methylenedioxybromobenzene reacts analogously, forming (*E,E*)-piperic acid in 60% yield. Sorbic acid and bromobenzene reacted poorly under a variety of conditions, giving mixtures of products which were not characterized.



trans-β-Bromostyrene and (*E*)-2,4-pentadienoic acid reacted normally to form (*E,E,E*)-7-phenyl-2,4,6-heptatrienoic acid in 57% yield in 4 h. These and other reactions are summarized in Table I.

Conjugated dienes without the activating carbonyl group reacted less well under the above conditions. The catalyst apparently was converted into relatively stable π-allylic complexes which either decomposed slowly or not at all under the reaction conditions. This problem was partially overcome by using larger amounts of catalyst. For example, iodobenzene and isoprene gave a 52% yield of 1-phenyl-3-methyl-1,3-butadiene (phenylisoprene) when 5% palladium acetate and 10% triphenylphosphine were employed as the catalyst and triethylamine as the base. As in the reactions of vinylic halides with mono olefins reported previously[4] the aryl halide–con-

Table I. Arylation Reactions of Conjugated Dienes[a]

aryl halide, mmol	registry no.	diene, mmol	registry no.	amine, mmol	phosphine	time, h	products, % yield[b]	registry no.
bromobenzene, 10	108-86-1	(*E,E*)-2,4-pentadienoic acid, 10	21651-12-7	$(C_2H_5)_3N$, 25	P(*o*-tol)$_3$	20	(*E,E*)-5-phenyl-2,4-pentadienoic acid, 92	28010-12-0
3,4-methylenedioxybromobenzene, 10	2635-13-4	(*E,E*)-2,4-pentadienoic acid, 10		$(C_2H_5)_3N$, 25	P(*o*-tol)$_3$[c]	24	(*E,E*)-5-(3′,4′-methylenedioxyphenyl)-2,4-pentadienoic acid, 60	136-72-1
(*E*)-β-bromostyrene, 10	588-72-7	(*E,E*)-2,4-pentadienoic acid, 10		$(C_2H_5)_3N$, 25	P(*o*-tol)$_3$	4	(*E,E,E*)-7-phenyl-2,4,6-heptatrienoic acid, 57	10576-63-3
iodobenzene, 10	591-50-4	isoprene, 30	78-79-5	$(C_2H_5)_3N$, 35	PPh_3[d]	18	(*E*)-1-phenyl-3-methyl-1,3-butadiene, 52	68036-69-1
bromobenzene, 10		isoprene, 12.5		piperidine,[h] 300	P(*o*-tol)$_3$	48	(*E*)-1-phenyl-3-methyl-1,3-butadiene, 35	
							N-1-(4-phenyl-2-methyl-2-butenyl)piperidine, 57	68036-70-14
bromobenzene, 10		1,3-cyclohexadiene, 15	592-57-4	piperidine, 300	PPh_3	16	phenylcyclohexadienes, 13[e]	
							3-phenyl-6-piperidino-1-cyclohexene, 51	68036-71-5
							4-phenyl-3-piperidino-1-cyclohexene, 2	68036-72-6
							1,4-diphenyl-1,3-cyclohexadiene, 2	10345-94-5
4-bromoanisole, 10	104-92-7	(*E*)-1,3-pentadiene, 25	2004-70-8	morpholine,[h] 300	PPh_3	8	1-*p*-anisyl-1,3-pentadiene, 57	3909-98-6
							1-*p*-anisyl-4-morpholino-3-pentene, 12[f]	68036-73-7
3-bromopyridine, 50	626-55-1	1,3-butadiene, 125	106-99-0	morpholine, 150	P(*o*-tol)$_3$	3	1-(3′-pyridyl)-4-morpholino-2-butene, 60[g]	68036-74-8

[a] 1 mol % of palladium acetate and 2 mol % of triarylphosphine based upon the aryl halide were used as catalyst except where noted. [b] Yields of isolated products. [c] 6 mol % of tri-*o*-tolylphosphine was used in this reaction with 1 mol % of $Pd(OAc)_2$. [d] 5 mol % of palladium acetate and 10 mol % of triphenylphosphine were used as catalyst in this example. The experiment was carried out by H. A. Dieck. [e] Two isomers present. The UV spectra of samples isolated by preparative GC indicate that they are 1-phenyl-1,3-cyclohexadiene and 3-phenyl-1,4-cyclohexadiene (registry no. 15619-32-6 and 4794-05-2, respectively). [f] 22% of 4-bromoanisole was recovered in this reaction. Yields of products are based on the total amount of 4-bromoanisole initially added. [g] 4 mmol of *N*-1-(2,7-octadienyl)morpholine (registry no. 25017-06-5) was also isolated. [h] Registry no.: piperidine, 110-89-4; morpholine, 110-91-8.

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