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Intramolecular Heck Reaction: Synthesis of Potential Antiinflammatory Agents

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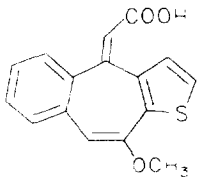
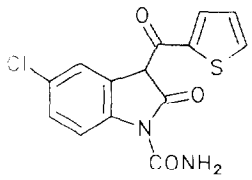
Abstract *An intramolecular Heck reaction is performed with palladium acetate on iodoethylenic ester* ***9b*** *to afford in good yield the tetracyclic ethylenic ester* ***6*** *which gave access to potential antiinflammatory agents.*

Inflammation results in part from the activation of interleukin-1β (IL-1β) from monocytes and macrophages and its release into the bloodstream through the action of interleukin-1β converting enzyme (ICE).[1] Drugs that inhibit this enzyme represent a new therapeutic approach for the treatment of inflammation, without the well-known side effects of NSAI drugs.[2] or degenerative neuronal diseases such as rheumatoid arthritis, Alzheimer's and Parkinson's diseases. Two substances IX207-887 (**1**)[3] and Tenidap (**2**),[4] reported to inhibit the release of IL-1, have retained our attention.

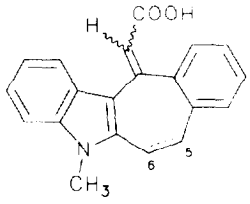


1



2

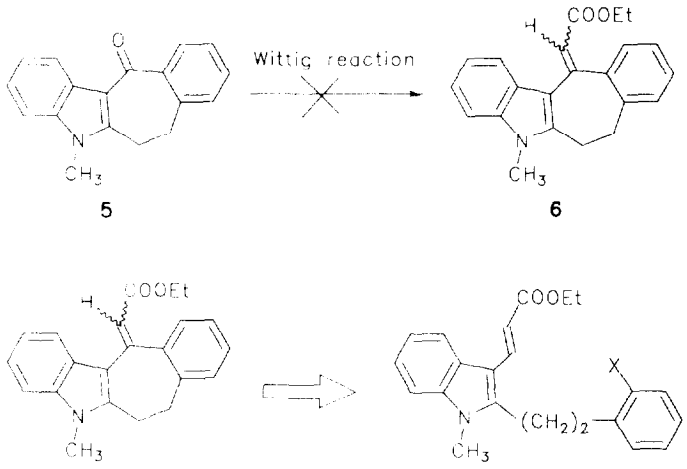
Taking the above structures into consideration, we have here described the synthesis of a new family of compounds possessed of both an indolic and a phenyl ring around a central seven-membered ring bearing an acetic acid side chain, enabling to obtain the previously unknown tetracyclic compounds **3** and **4** as candidates for potential new antiinflammatory drugs.



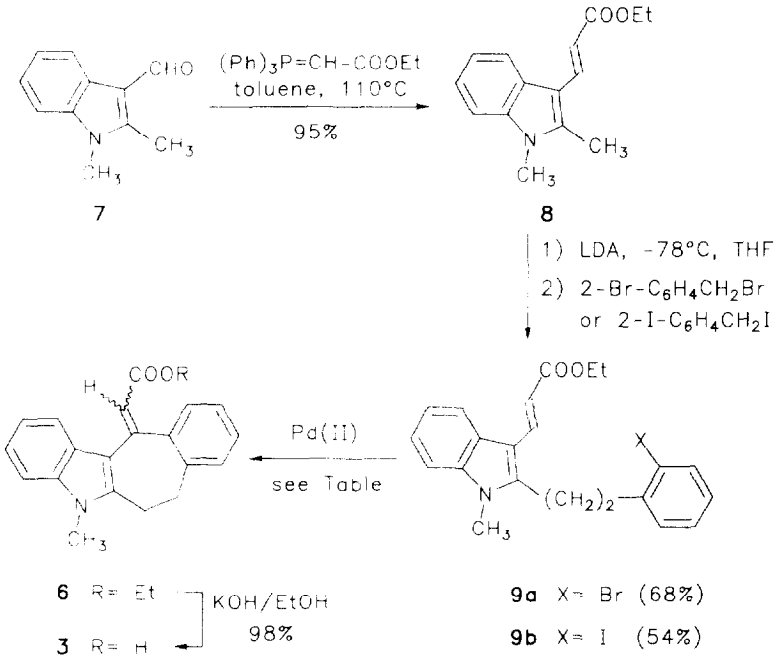
3: C_5-C_6 single bond
4: C_5-C_6 double bond

In our laboratory we had previously tried without success to obtain intermediate **6** by a Wittig reaction on ketone **5**, prepared in five steps from commercially available 1-methylindole.[5]

So, we planned a second synthetic route, with a Heck annulation,[6] in order to create the 7-membered ring of compound **6**.



The synthesis of the ester **6** and acid **3** from the easily available starting material 3-formyl-1,2-dimethylindole **7**[7] is outlined in Scheme 1.



Scheme 1

Indole **7** was treated with (carbethoxymethylene)triphenylphosphorane at reflux of toluene to give the α,β ethylenic ethyl ester **8** as *E* isomer in 95% yield. Chemoselective metallation of the methyl in 2-position of **8** was achieved with LDA in THF at low temperature, followed by treatment with 2-bromobenzyl bromide to give **9a** (68%) or with freshly prepared 2-iodobenzyl iodide to afford **9b** (55%). In the same way, experimentation with the commercially available 2-iodobenzyl chloride gave a low yield of desired alkylated product **9b.**

Attempts of cyclization from the bromo derivative **9a** using different conditions for Heck reaction failed in all cases; the starting material **9a** remained unchanged. Nevertheless, good and variable yields of **6** were obtained from the iodo derivative **9b** (see table).

Table: Synthesis of **6** by Heck reaction from **9b**.

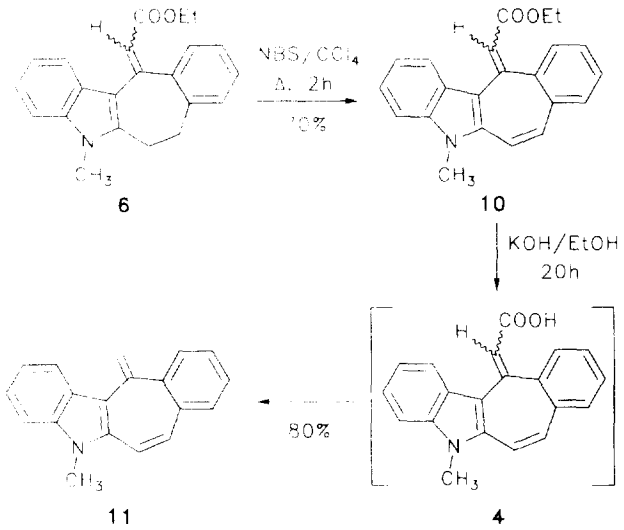
Palladium catalyst	Ligands added	Base	Solvent	Yield (%)
$Pd(OCOCH_3)_2$ (0.1 eq.)	Ph_3P (0.2 eq.)	$(CH_3COO)_2Tl$ (2 eq.)	CH_3CN	20
$Pd(OCOCH_3)_2$ (0.05 eq.)	Ph_3P (0.2 eq.)	K_2CO_3 (2 eq.)	CH_3CN	36
$(PPh_3)_4Pd$ (0.05 eq.)	/	K_2CO_3 (5 eq.)	CH_3CN	42
$(PPh_3)_2PdCl_2$ (0.05 eq.)	/	$(CH_3CH_2)_3N$	$(CH_3CH_2)_3N$	70
$Pd(OCOCH_3)_2$ (0.2 eq.)	Dppp (0.4 eq.)[a]	K_2CO_3 (5 eq.)[b]	CH_3CN	83[8]

a) Dppp = 1,3-bis-(diphenylphosphino)propane.

b) Triethyl benzylammonium chloride (0.15 eq.) was also added.

From the cyclization reaction, a mixture of *E/Z* stereomers of **6**,[9] separated by column chromatography, was obtained where the *E* isomer was initially predominant (8:2 *E/Z* ratio) in accordance with the usual tenets of *cis*-addition and *syn* elimination of the Heck reaction.[10] At room temperature, the *E* isomer of **6** was slowly equilibrated into a mixture of stereomers (3:7 *E/Z* ratio).[11] Finally, saponification of the ester **6** (mixture of stereomers) gave the acid **3**[12] (1:1 *E/Z* ratio, not separable) in 98% yield.

An attempt at obtaining the unsaturated acid **4** from the ethylenic ester **6** is described in Scheme 2.



Scheme 2

Bromination of *E*-isomer **6** with one equivalent of *N*-bromosuccinimide and subsequent spontaneous dehydrobromination (without addition of base) in boiling CCl_4 gave **10** (3:2 *E/Z* ratio).[13] The use of AIBN in this reaction gave a mixture of brominated products. Alkaline hydrolysis of **10** afforded the unstable acid **4** which spontaneously lost CO_2 to give **11**.[14,15]

This work shows that iodoethylenic ester **9b** is an excellent precursor through an intramolecular Heck reaction to obtain the potent antiinflammatory tetracyclic acid **3**. Due to the behavior of the acid **4**, we are investigating the metallation of the ethylenic carbon of the ester **10** in order to obtain more stable compounds.

References and notes

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8. Representative procedure: To a solution of indole **9b** (300 mg, 0.65 mmol) in CH_3CN (15 ml) was added palladium acetate (186 mg, 0.13 mmol), Dppp (109 mg, 0.26 mmol), K_2CO_3 (451 mg, 3.25 mmol) and triethylbenzyl ammonium chloride (23 mg, 0.1 mmol). The mixture was then stirred at reflux for 4 days. After cooling, the solvent was evaporated. The crude product was purified by chromatography on silica gel (EtOAc/ petroleum ether 3:7 as eluent) to afford **6** (*Z* isomer: 36 mg; *E* isomer: 144 mg; 83% overall yield).
9. **6** (*Z* isomer): mp 170-172°C (dichloromethane/petroleum ether); IR (KBr) 1685 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, 3H, J = 7.3 Hz, O-CH_2-CH_3), 2.87 (m, 4H, -CH_2-CH_2-), 3.60 (s, 3H, N-CH_3), 4.11 (q, 2H, J = 7.3 Hz, O-CH_2-CH_3), 6.49 (s, 1H, =CHCOOC_2H_5), 7.08-7.35 (m, 7H, H_{ar}), 7.92-7.95 (m, 1H, H_{ar}).
6 (*E* isomer): mp 218-220°C (*n*-butanol); IR (KBr) 1685 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.10 (t, 3H, J = 7.3 Hz, O-CH_2-CH_3), 2.87 (m, 4H, -CH_2-CH_2-), 3.59 (s, 3H, N-CH_3), 4.11 (q, 2H, J = 7.3 Hz, O-CH_2-CH_3), 6.18 (s, 1H, =CHCOOC_2H_5), 7.08-7.35 (m, 8H, H_{ar}).
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11. Determined by analysis of NMR spectra.
12. **3**: mp 231-233°C (EtOAc); IR (KBr) 3600-3000 (br), 1660 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.80-3.40 (m; 4H; -CH_2-CH_2-), 3.61 (s, 3H, N-CH_3), 6.02 (s, 0.5H, (*E*)=CHCOOH), 6.30 (s, 0.5H, (*Z*)=CHCOOH), 7.01-7.85 (m, 8H, H_{ar}).
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14. **11**: mp 127-129°C (dichloromethane/methanol); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.74 (s, 3H, N-CH_3), 5.38 and 5.61 (d, 1H, J = 1.5 Hz, =CH_2), 6.81 and 6.90 (d, 1H, J = 11.8 Hz, -CH=CH-), 7.13-8.05 (m, 8H, H_{ar}).
15. All compounds gave correct mass spectra or elemental analyses (C, H, N).

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