

PALLADIUM-CATALYZED CARBONYLATION OF ENOL TRIFLATES.
A NOVEL METHOD FOR ONE-CARBON HOMOLOGATION OF KETONES
TO α,β -UNSATURATED CARBOXYLIC ACID DERIVATIVES

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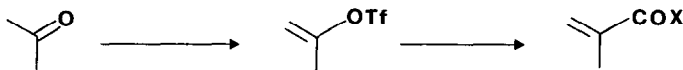
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Abstract: Ketones can be homologated to α,β -unsaturated esters or amides via their enol triflates by a palladium-catalyzed reaction with carbon monoxide and alcohols or amines.

Synthetic methodologies which result in the nucleophilic carboxylation of a carbonyl group to a higher carboxylic acid derivative together with elaboration of the original electrophilic centre (e.g. the introduction of α,β -unsaturation) are of particular value.¹

Enol triflates, easily available from ketones by treatment with triflic anhydride and 2,6-di-*t*-butyl-4-methylpyridine,² have been first reported by us to undergo oxidative addition to palladium(0).³ The resulting vinylpalladium(II) triflates were then able to insert⁴ a variety of olefins to form coupling products^{3a} and react with trialkylammonium formate to give alkenes.^{3b}

In this letter, we wish to present a successful synthesis of α,β -unsaturated esters or amides from vinyl triflates, carbon monoxide, and alcohols or amines in the presence of a palladium catalyst.



X = OR, NR₂

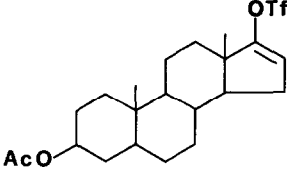
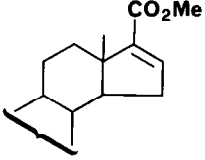
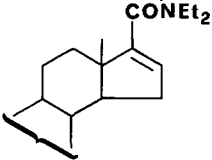
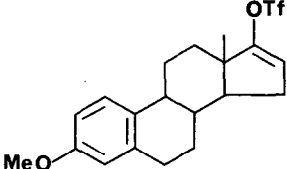
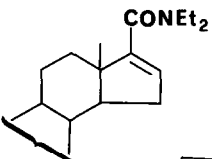

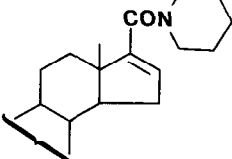
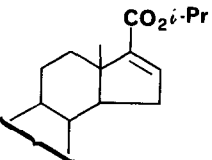
The following procedure is illustrative. A mixture of 3 β -acetoxy-5 α -androst-16-en-17-yl triflate (464 mg, 1 mmol), triethylamine (0.28 ml, 2 mmol), palladium acetate (6 mg, 0.03 mmol), triphenylphosphine (16 mg, 0.06 mmol), and MeOH (1.8 ml, 40 mmol) in DMF (4 ml) was purged with carbon monoxide for 5 min and

Table. Palladium-Catalyzed Carbonylation of Enol Triflates^a

| Entry | Enol Triflate ^{b,c} | Alcohol or Amine | Reaction time (h) | Carbonylation ^c Product | Yield ^d (%) |
|-------|------------------------------|--------------------|---------------------|------------------------------------|------------------------|
| 1 | | MeOH | 2.5 ^e | | 76 |
| 2 | " | Et ₂ NH | 24 ^f | | 84 |
| 3 | | MeOH | 2 ^{e,g} | | 75 |
| 4 | | " | 4.5 | | 79 |
| 5 | " | Et ₂ NH | 6 | | 69 |
| 6 | | MeOH | 3 | | 83 |
| 7 | | " | 6 | | 75 |
| 8 | | " | 3.75 ^{e,g} | | 90 |

(continued)

Table (continued).

| Entry | Enol Triflate ^{b,c} | Alcohol or Amine | Reaction time (h) | Carbonylation ^c Product | Yield ^d (%) |
|-------|---|--|-------------------|--|------------------------|
| 9 |  | MeOH | 1.5 |  | 77 |
| 10 | " | Et ₂ NH | 1 |  | 91 |
| 11 |  | " | 1 |  | 74 |
| 12 | " |  | 1 |  | 98 |
| 13 | " | iPrOH | 1 |  | 85 |

^a Carried out in the same manner as described in the text, unless otherwise noted. Addition of Et₃N was omitted in the amidation reactions. Disappearance of starting material was monitored by TLC. ^b Enol triflates were prepared according to ref. 3. ^c All new compounds were adequately characterized spectroscopically (IR, ¹H NMR, MS). ^d Yields of isolated material and referring to single non optimized runs. ^e Reaction performed at 45 °C. ^f CH₂Cl₂ was used as the solvent. ^g CHCl₃: DMF = 5 : 1 was used as the solvent.

stirred under a CO balloon at room temperature for 1.5 h. Ether and water were then added. The ether layer was washed with water until neutral, dried (Na₂SO₄), and evaporated. The residue (400 mg) was chromatographed on silica gel (12 g, hexane : dichloromethane = 3 : 2 as eluant) to give 290 mg (77%) of methyl 3 β -acetoxy-5 α -androst-16-ene-17-carboxylate (entry 9): mp 191.5–193.5 °C (acetone - MeOH); $[\alpha]_D^{25}$ (CHCl₃, 1%) +14° (lit.⁵ mp 194–196 °C; $[\alpha]_D^{25}$ +16°); IR (KBr) 1730, 1711, 1595 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (3H, s, 13-Me), 0.88 (3H, s, 10-Me), 1.98 (3H, s, 3 β -OAc), 3.72 (3H, s, CO₂Me), 4.7 (1H, m, 3 α -H), 6.78 (1H, m, C-16

H); MS, m/e (relative intensity) 374 (parent, 4), 359 (17), 315 (44).

As shown in the table, the carbonylation of enol triflates proceeded uniformly in good yield and provides a practically useful route to α,β -unsaturated esters and amides which competes favourably with related procedures⁶ in terms of mildness and/or availability of precursors.

We eventually found that 3-methoxy-19-norpregna-1,3,5(10),16-tetraen-17-yl triflate was converted at room temperature to the corresponding 17-carboxylic acid in 87% yield by treatment with triethylammonium formate^{3b} and carbon monoxide in the presence of usual palladium catalyst.



Intermediacy of a mixed anhydride according to the mechanistic scheme proposed for the palladium-catalyzed carboxylation of arenediazonium salts⁷ can reasonably account for the above result.

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