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ADDITION OF FUNCTIONALIZED ALLYLIC BROMIDES TO TERMINAL ALKYNES

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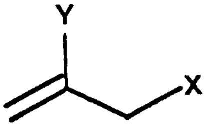
Summary -

Bromoesters 2a, 2b and bromophosphonates 2c, 2d add regioselectively to terminal alkynes in the presence of zinc to give the highly functionnalized dienes 4-7 which are cyclized to various six or seven membered carbo- or heterocycles.



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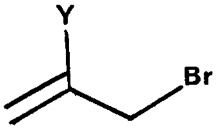

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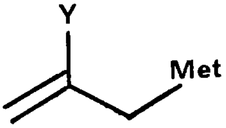

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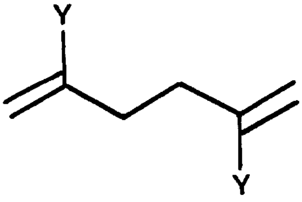

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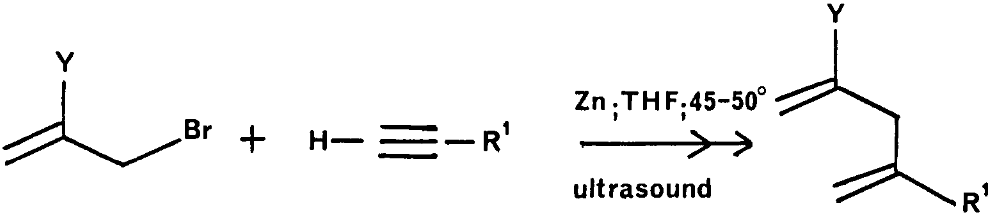
Y : functional group

Functionnal allylic systems of type 1 can react as electrophiles if X is a leaving group 1) or as nucleophiles if X is a metal ion2). The know carbometallation of alkynes with allyl anions (Y=H, alkyl ; X=Mg^{2+}, B^{3+}, Zn^{2+})3) led us to examine the reaction of the allylic bromides 2 with alkynes in the presence of a metal (Barbier conditions4) for the generation of the organometallic species 3). In such a reaction the following conditions should be met : (i) the Y function must be stable towards the allylic reagent 3 ; (ii) the preparation of 3 must be as mild as possible to prevent any self-coupling of the bromide 2 to the diene 4. We have found that if the esters 2a and 2b5) or the phosphonates 2c2b) and 2d6) are slowly added at 45-50° and in the presence of sonic wawes 7) to a THF solution of a terminal alkyne in the presence of zinc, the expected reaction occurs and the products 4, 5, 6 and 7 are isolated in fair to good yield (see table).



<u>2a</u> : Y=COOtert-C_4H_9
<u>2b</u> : Y=$COOC_2H_5$
<u>2c</u> : Y=$PO(OCH_3)_2$
<u>2d</u> : Y=$PO(OCH_2CH_3)_2$

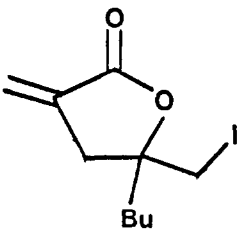
<u>4</u> : Y=COOtert-C_4H_9
<u>5</u> : Y=$COOC_2H_5$
<u>6</u> : Y=$PO(OCH_3)_2$
<u>7</u> : Y=$PO(OC_2H_5)_2$

Entry	<u>2</u>	R^1	Product	Yield[a]
1	<u>2a</u>	$-C_4H_9$	<u>4a</u>	70
2	"	$-CH_2OSiMe_3$	<u>4b</u>	81
3	"	$-CH_2CH_2OSiMe_3$	<u>4c</u>	70
4	"	$-CH_2O$ tert-C_4H_9	<u>4d</u>	64
5	"	$-CH\begin{cases}CH_3\\OSiMe_3\end{cases}$	<u>4e</u>	54
6	"	$-CH_2SC_6H_5$	<u>4f</u>	55
7		$-CH_2-CH(OC_2H_5)_2$	<u>4g</u>	60
8	<u>2b</u>	$-CH_2O$ tert.C_4H_9	<u>5a</u>	62
9	"	$-CH_2OSiMe_3$	<u>5b</u>	68
10	<u>2c</u>	$-C_4H_9$	<u>6a</u>	48
11	"	$-CH_2-OSiMe_3$	<u>6b</u>[b)]	72
12	"	$-CH_2CH_2OSiMe_3$	<u>6c</u>[b)]	66
13	<u>2d</u>	$-CH_2OSiMe_3$	<u>7a</u>[b)]	73
14	"	$-CH_2CH_2OSiMe_3$	<u>7b</u>[b)]	73

a) The yields given are those of distilled or flash chromatographically purified materials

b) This compound was desilylated during work-up and isolated as an alcohol

The addition is regiospecific but seems to be sensitive to steric hindrance[8] (compare entry 2 and 5). The presence of an oxygen atom α, or β to the triple bond, enhances the yield (compare entry 1, 2 and 10, 11, 14). We noticed that allyl bromide reacts under these "Barbier" conditions in the same way[9]. The highly functionnalized diene 4-7 can be used in various cyclization processes. Treatment of 4a with I_2/K_2CO_3[10] in THF at 25° C yields the α-methylene lactone 8 (90%). The trimethylsilyloxy-ester 4b



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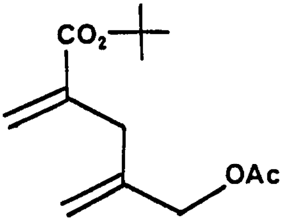

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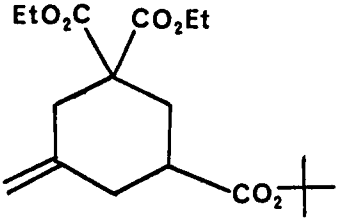

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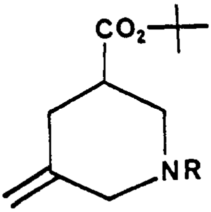
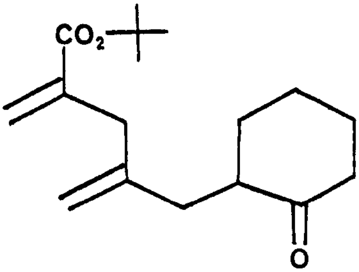
is acetylated with acetyl chloride in acetic acid (88%) to 9 which is the starting material for a Pd°[11] mediated synthesis of 6-membered carbo- and heterocycles. In the presence of a catalytic amount of $Pd(PPh_3)_4$ (5% mol.) and 1 eq. Et_3N, the sodium salt of diethylmalonate reacts with ester 9 (THF, 3h reflux) to give the triester 10 (70%). With primary amines (8% $Pd(PPh_3)_4$, 1.5 eq. Et_3N, 2 eq. RNH_2, 24 h reflux in THF) we obtained the piperidines 11a (82%) and 11b (77%)



11a : R=C_7H_{15}
11b : R=$CH_2C_6H_5$



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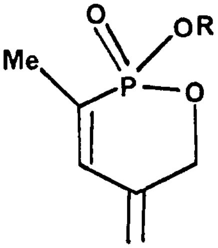
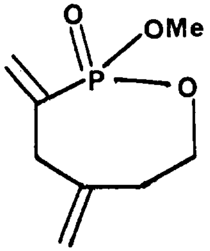


13a : R=CH_3
13b : R=C_2H_5



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The reaction of 9 with an enamine : 1-pyrrolidino-1 cyclohexene in acetonitrile at 25°, in the presence of 10 mol % $Pd(PPh_3)$ and 2 equiv. Et_3N, leads to the open-chain keto-ester 12 in modest yield (50%).

The phosphonates 6b, 7a are converted to the heterocycles 13a and 13b by treatment in THF with a catalytic amount of NaH (4 min. at 25°) in quantitative yield, whereas 6c gives the unconjugated seven membered ring 14 (3 days, NaH in THF, 78%).

Carbometallation of alkynes with other functionnalized allylic systems of type 1 (for example Y=$SiMe_3$) and applications of the formed dienes are currently investigated.

Typical procedure -

A 100 ml flask was charged under nitrogen with 2.6 g (40 mmol) of zinc (purity 99.999%), 1.5 g (8 mmol) dibromoethane and 7 ml of dry THF. This mixture was shortly boiled to start the formation of $ZnBr_2$. After 0.25 h, 3.07 g (24 mmol) of propargyltrimethylsilylether was added rapidly and the flask was immersed in a common laboratory cleaner filled with warm water (55°) Then a solution of 4 g (18.1 mmol) of tert-butyl α-(bromomethyl) acrylate in 12 ml THF was added over 0.75 h. The reaction temperature was maintained between 45° and 50° during the addition. After 10-20 min (VPC control) at 45°, the white-yellow solution was cooled at 0° and 20 ml of aq. NH_4Cl solution and 50 ml ether were added. After filtration, the organic layer was washed with NaCl solution, dried over $MgSO_4$ and filtered. After distillation 3.76g-3.94g (77%-81%) of pure 4b are obtained (72°/10^{-2} mmHg).

Acknowledgements -

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References and Notes -

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8) The formation of diene 4 (Y=COO tert-butyl and $COOC_2H_5$) is favoured as the steric hindrance of the alkyne is increased.

9) We have isolated 2-hexyl-1,4-pentadiene in 64% yield from allyl bromide and 1-octyne. With preformed allylzinc bromide an excess of the reagent seems to be necessary : M. Gaudemar, C.R. Acad. Sci. Paris, 273, Série C, 1669 (1971) and F. Bernadou, B. Mauzé, L. Miginiac, C.R. Acad. Sci. Paris, 276, Série C, 1645 (1973).

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