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A NOVEL METHOD FOR THE ISOPRENYLATION OF β-DICARBONYL COMPOUNDS

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ABSTRACT :

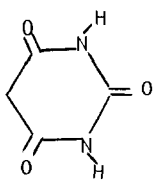
The water-soluble composition rhodium/tris (sodium 3-sulfophenyl) phosphine (TPPTS) selectively catalyses the condensation of isoprene with active methylene compounds. An efficient synthesis of isofeprazone is described.

Many biologically active substances are "mero-terpenoïds", i.e. contain in their structure an isoprenyl group (1), for instance, on the ring of a phloroglucinol sub-structure, or on the central atom of a β-dicarbonyl substrate. Synthesis of these structures is usually carried out by isoprenylation with the formal γ,γ-dimethylallyl cation (2). However different problems arise :

- A mixture of the monosubstituted and disubstituted compounds is obtained.
- Double bond isomerization : terminal and internal.
- Lack of regioselectivity because of the reactivity of the allylic cation at C_1 or C_4.

We found that the use of isoprene as the alkylating agent and a catalyst comprised of a water-soluble phosphine developed in our laboratories (3), tris (sodium 3-sulfophenyl) phosphine (TPPTS) and rhodium-I, gave the required selectivity and regiospecificity efficiently.

Isoprene (1 equivalent) reacts at room temperature with barbituric acid (1 equivalent 1, in a H_2O/CH_3OH (75/25) mixture catalyzed by Rh^{I}/TPPTS/Na_2CO_3. Compounds 2 and 3 were isolated in 50 % overall yield and a 2/3 molar ratio of 35/65. 2 and 3 show numerous tautomeric forms in solution (4). Under our conditions, partial double bond isomerization was observed (5).



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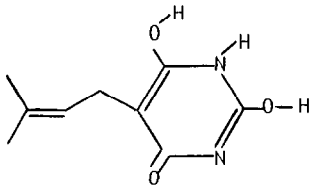
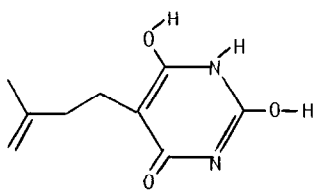
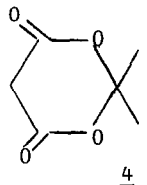


2



3

Meldrum's acid 4 reacts under similarly mild conditions to give the monosubstituted derivative 5 with no isomerization of the double bond (60 % isolated yield) (6).



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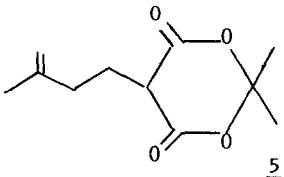
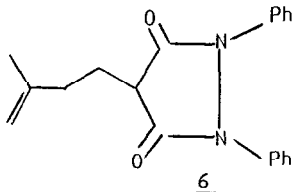
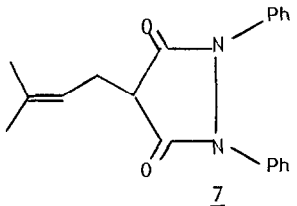


5

Taking advantage of this reaction, a new and efficient synthesis of isofeprazone 6 was developed, starting from isoprene and readily available 1,2-diphenyl 3,5-dioxopyrazolidine (7). Isofeprazone 6 and especially its isomer feprazone 7 are potent anti-inflammatory substances with weak ulcerogenic properties (8).



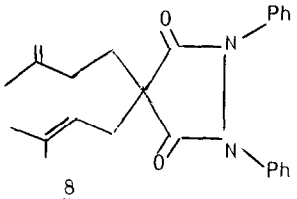
6



7

Isomerization of 6 to 7 is easily carried out with Pd/C, $PdCl_2(PhCN)_2$ type catalysts (5).

Under more vigorous conditions (100°C, 16 h, H_2O/C_2H_5OH) double substitution occured, giving a mixture of isomers 8, 9 and 10 in quantitative yield (9).



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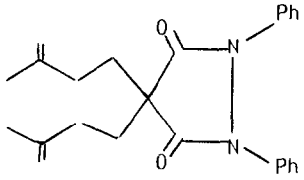

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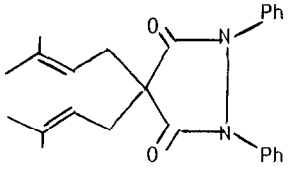

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The addition of activated methylene compounds to disymmetric dienes such as isoprene is generally poorly regioselective (10). However, the use of a Rh^I/ TPPTS system permits this reaction to be very selective with exclusive attack on the monosubstituted double bond. Since the catalytic system is water soluble, it is easily separated from the organic layer and recycled without any loss of activity.

Preparation of isofeprazone 6 : (11).

In a 500 ml round bottomed flask, was placed 55.5 g (220 mMol) 1,2-diphényl 3,5-dioxopyrazolidine, 0.41 g (Rh Cl COD)$_2$, 6.02 g tris (sodium 3-sulfophenyl) phosphine and 1.5 g of Na_2CO_3. Air was replaced by argon and then 200 ml water, 50 ml methanol and 22 ml (220 mMol) isoprene were added. The reaction medium was magnetically stirred 48 H at 25°C. A white precipitate formed, which was filtered and washed with water. 61.7 g of 6 was obtained (87 % yield).

m.p. 128 - 130°C (lit. (8) 125-126°C).

Acknowledgment : We are grateful for the technical assistance of F. GRASS.

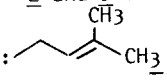
(1) J.W. Cornforth, Chem. in Britain 4, 102 (1968).

(2) V.K. Ahluwalia, K.K. Arora, and R.S. Jolly, J. Chem. Soc. Perkin I, 335 (1982).

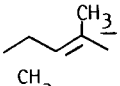
(3) a) E.Kuntz (RHONE-POULENC) - French Patent 2,314,910 (20.6.75).

b) RHONE-POULENC - European Patent 44,771 (11.5.81).

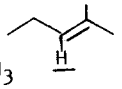
(4) 2 and 3 : H NMR (360 MHz, DMSO d_6, ppm, HMDS) :



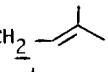
(s) 1.47;



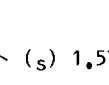
(s) 1.56 ;



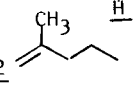
(t) 4.82 ;



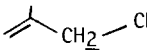
(d) 2.45 ;



(s) 1.57 ;

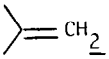
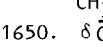


(s) 4.61 et 4.55 ;



(m) 1.90 et 1.75 . IR (KBr, cm^{-1}).
ν C = O : 1770-1700 ; νNH(OH) : 3750 - 3200.MS : m/z(%):264 (7), 221 (16), 196 (78), 141 (100), 128 (64), 69 (47), 56 (32), 42 (86), 41 (46).

(5) BASF. German Patent 1,267,682 (22-9-67).

(6) a) 5 : m.p. 90°C, H NMR (360 MHz, $CDCl_3$, ppm, HMDS) :  (s) 4.73 et 4.67 ; - CH_3 (s) 1.68 ; - CH_2 - CH_2 - CH< (m) 2.20 ; $-CH_2-CH_2-CH<$ (m) 2.20 ; $-\underset{|}{C}-\underline{H}$ (m) 3.48 ;  (s) 1.69 et 1.72 IR (KBr, cm^{-1}) ν C = O : 1800-1750 ; νC = C : 1650. δC = CH_2 : 890.
MS : m/z (%) : 155 (25), 154 (27), 137 (33), 136 (35), 109 (23), 108 (22), 95 (21), 82 (21), 81 (24), 68 (100), 67 (55), 55 (80), 43 (75), 39 (33), 27 (69).

b) Mitsui Petrochemical Industries, Ltd.
Japanese Patent 8,059,181 (30.10.78)

(7) a) H.Ruhkopf, Ber. 77, 820 (1940)

b) M. Hruby - Czechoslovak Patents 129,345 (15•10•68), 129,346 (15•10•68), 129,347 (15•10•68).

(8) a) G.Pala, S. Casadio, E. Marazzi - Uberti, B. Lumachi, E. Crescenzi, A.Donetti, A. Mantegani and C. Bianchi, Arzneim. - Forsch. (Drug Res.) 22, 171, 174, 177, 183, 191 (1972).

(b) E. Cereda, E. Bellora and A. Donetti, Tetrahedron Lett 21, 4977 (1980).

(c) Istituto de ANGELI S.P.A. French Patent 2,515,646 (29.10.82).

(9) 8, 9 and 10 :
HNMR (360 MHz, $CDCl_3$, ppm, HMDS) : - CH_3 (s), 1.49, 1.52, 1.62 ; -CH_2 - CH_2 (m) 1.98 ; - CH_2 - CH_2 (m) 1.98 ; $\geq C = CH - CH_2 -$ (d) 2.56 ; $\geq C = CH_2$ (s), 4.61 et 4.62 ; $\geq C = CH -$ CH_2 (t) 4.99 ; PHENYL 7.11 to 7.25. ratio $\geq C = C <$ terminal/ $\geq C = C <$ internal = 1,6. IR (KBr, cm^{-1}) $\nu C = O$: 1755 and 1720 ; $\nu C = C$: 1650; ν $C = CH_2$: 900 ; ν Ar : 1600 and 1500 ; mono substitution : 700 and 760.
MS : m/z (%) 388 (45), 320 (24), 265 (100), 264 (71), 212 (7), 211 (12), 195 (6), 183 (22), 77 (90), 69 (31), 41 (51).

(10) R. Baker, Chem. rev. 73, 487 (1973).

(11) 6 . HNMR (360 MHz, $CDCl_3$, ppm, HMDS) : - CH_3 (S)1.67 ;  (s) 4.70 ; - CH_2 - CH_2 - $\underset{|}{\overset{|}{C}}$ - H (m) 2.23 - 2.17 ; - $\underset{|}{\overset{|}{C}}$ - H (t) 3.36 ; Phenyl (m) 7.23 and (m) 7.09. IR (KBr, cm^{-1}) $\nu C = O$: 1750 - 1720 ; $\nu C = C$: 1650 ; $\nu C = CH_2$: 890 ; Phenyl : 1595 - 1490 / 700-750. MS : m/z (%) : 320 (29) , 265 (32), 264 (100), 252 (18), 184 (19), 183 (50), 105 (13), 77 (86).

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