Chinese Chemical Letters Vol. 14, No. 3, pp 221 – 224, 2003
http://www.imm.ac.cn/journal/ccl.html

Condensation Reaction of 5, 6-Dihydro-6-methyl-6-piperonyl-2*H*-pyran-2, 4-dione, Ethyl Orthoformate and Substituted Anilines

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Abstract: Piperonyl methyl ketone was obtained by oxidizing isosafrole with hydrogen peroxide and formic acid. Dianion of ethyl acetoacetate reacted with piperonyl methyl ketone and 5, 6-dihydro-6-methyl-6-piperonyl-2*H*-pyran-2, 4-dione was prepared, which reacted with substituted anilines in the presence of ethyl orthoformate to obtain 3-anilinomethylene-5, 6- dihydro-6-methyl-6-piperonyl-2*H*-pyran-2, 4-diones. Their structures were confirmed by ^{1}HNMR and elemental analysis.

Keywords: Piperonyl methyl ketone, isosafrole, dianion.

5,6-Dihydro-pyran-2,4-dione derivatives have interesting biological activities. Two American companies (Pharmacia & Upjohn, Park-Davis Division of Warner-Lambert) had reported 5,6-dihydro-2*H*-pyran-2,4-dione derivatives have good inhibitory activity of HIV proteases[1-3]. Recently we have reported 3-anilinomethylene-5, 6-dihydro-6-alkyl(aryl)-2*H*-pyran-2,4-dione derivatives have interesting fungicidal, tobacco virucidal activities[4-5]. The results led us to study the biological activities of different 5, 6-dihydro-2*H*-pyran-2, 4-dione derivatives. We reacted 5, 6-dihydro-6-methyl-6-piperonyl-2*H*-pyran-2, 4-dione which was obtained by reacting dianion of ethyl acetoacetate with piperonyl methyl ketone with substituted anilines in the presence of ethyl orthoformate and new condensation products **3** were obtained.

In a general procedure, isosafrole was added dropwise to a solution of hydrogen peroxide and formic acid in the presence of 1,2-dichloroethane at 40-45°C. After the addition, the mixture was continued to stir for 2h, the organic phase was separated from the solution and the solution was extracted two times with 1,2-dichloroethane. The solvent was evaporated under the reduced pressure. The crude product was hydrolyzed with 15% diluted sulfuric acid for 3h and piperonyl methyl ketone was obtained. Dianion of ethyl acetoacetate, which was obtained by reacted ethyl acetoacetate with NaH and ^{n}BuLi, reacted with piperonyl methyl ketone in the presence of absolute anhydrous THF for 6h at 0°C, and the slurry was poured into ice-cooled water. The solution was allowed to stir overnight and acidified with 5% diluted hydrochloride to obtain 5,6-dihydro-6-methyl-6-piperonyl-2*H*-pyran-2,4-dione. We reacted 5,6-

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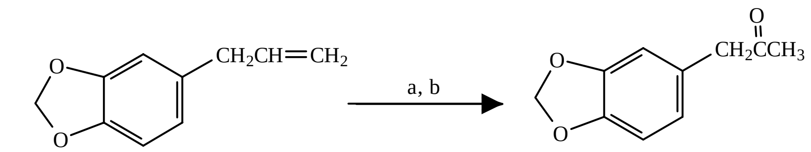
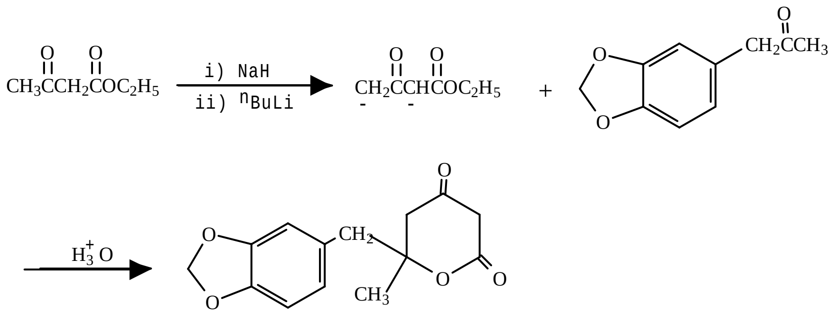
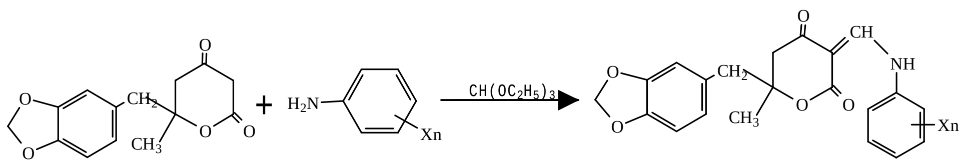


a) $HCOOH/H_2O_2$; b) H^+_3O.

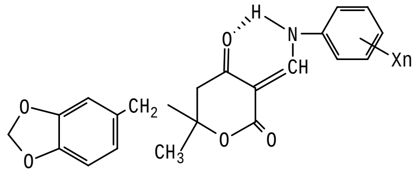




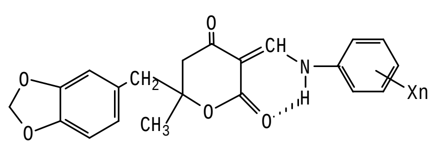
1 **2** **3**

dihydro-6-methyl-6-piperonyl-2*H*-pyran-2,4-dione(**1**) with substituted anilines(**2**) in the presence of ethyl orthoformate at 85-90°C and the products **3** were obtained. The products **3** were purified by silica gel column or recrystallization (**Table 1**). Their structures were confirmed by ^{1}HNMR (**Table 2**) spectra and elemental analysis (**Table 1**).

The products **3** that were confirmed by ^{1}HNMR spectra, are composed of a pair of isomers **Z** and **E**, probably due to intramolecular hydrogen bonds. The chemical shifts of hydrogen on nitrogen atom and carbon-carbon double bond of **Z** lie in lower field because of the electron-withdrawing effect of oxygen atom.



Z-**Form**



E-**Form**

Table1 Prepared data and elemental analysis data of 3-anilinomethylene-5,6-dihydro-6-methyl-6-piperonyl-2*H*-pyran-2,4-diones **3**

Compound	Xn	Yield（%）	m.p(°C)	Elemental analysis(%, Cacl.)		
				C	H	N
a	4-CH_3	74.9	149-151	69.64(69.66)	5.27(5.54)	4.03(3.69)
b	4-Cl	70.2	182-184	62.96(63.08)	4.52(4.51)	3.35(3.50)
c	4-Br	80.1	189-191	56.67(56.76)	4.16(4.05)	3.10(3.15)
d	H	66.4	173-175	68.83(69.04)	5.25(5.21)	3.83(3.84)
e	3,4-Cl_2	75.7	148-150	57.90(58.06)	3.94(3.92)	3.15(3.23)
f	2,5,6-Cl_3	79.6	198-200	53.76(53.79)	3.38(3.42)	2.70(2.99)
g	2-CH_3	64.3	117-119	69.65(69.66)	5.65(5.54)	3.68(3.69)
h	2-Br	82.7	157-159	56.93(56.76)	3.91(4.05)	2.93(3.15)
i	4-OCH_3	78.8	156-157	66.72(66.84)	5.19(5.32)	3.76(3.54)
j	2-OCH_3	68.7	168-170	66.77(68.84)	5.27(5.32)	3.60(3.54)
k	2-CH_3-4-Cl	71.5	163-165	63.66(63.85)	5.12(4.84)	3.38(3.39)
l	2,6-$(CH_3)_2$	67.8	Oil	70.32(70.23)	5.51(5.85)	3.33(3.56)
m	2-CH_3-6-C_2H_5	62.6	Oil	70.60(70.76)	5.99(6.14)	3.35(3.44)

Table 2 ^{1}HNMR data of 3-anilinomethylene-5,6-dihydro-6-methyl-6- piperonyl-2*H*-pyran-2, 4-diones **3**

compound	^{1}HNMR, δ, J_{H-H}/Hz
a	1.43(s, 3H), 2.34(s, 3H), 2.80(m, 4H), 5.89(s, 2H), 6.71(m, 3H), 7.19(m, 4H), 8.52(dd, 1H, J=12.0), 11.45(d, J=14.0), 12.45(d, J=14.0)
b	1.42(s, 3H), 2.74(m, 4H), 5.89(s, 2H), 6.70(m, 3H), 7.19(m, 4H), 8.51(dd, 1H, J=12.8), 11.45(d, J=14.0), 12.45(d, J=14.0)
c	1.42(s, 3H), 2.88(m, 4H), 5.90(s, 2H), 6.75(m, 3H), 7.20(m, 4H), 8.49(dd, 1H, J=11.4), 11.44(d, J=14.6), 12.43(d, J=14.6)
d	1.43(s, 3H), 2.70(m, 4H), 5.90(s, 2H), 6.71(m, 3H), 7.24(m, 5H), 8.55(dd, 1H, J=11.4), 11.49(d, J=12.6), 12.45(d, J=12.6)
e	1.46(s, 3H), 2.91(m, 4H), 5.93(s, 2H), 6.73(m, 3H), 7.37(m, 3H), 8.42(dd, 1H, J=10.8), 11.41(d, J=13.6), 12.39(d, J=13.6)
f	1.44(s, 3H), 2.70(m, 4H), 5.88(s, 2H), 6.70(m, 3H), 7.53(m, 3H), 8.42(dd, 1H, J=10.4), 11.82(d, J=12.6), 12.68(d, J=12.6)
g	1.43(s, 3H), 2.39(s, 3H), 2.78(m, 4H), 5.86(s, 2H), 6.70(m, 3H), 7.23(m, 4H), 8.56(dd, 1H, J=10.8), 11.71(d, J=13.6), 12.45(d, J=13.6)
h	1.43(s, 3H), 2.88(m, 4H), 5.87(s, 2H), 6.72(m, 3H), 7.35(m, 4H), 8.52(dd, 1H, J=10.8), 11.88(d, J=14.6), 12.76(d, J=14.6)
i	1.42(s, 3H), 2.87(m, 4H), 3.79(s, 3H), 5.88(s, 2H), 6.70(m, 3H), 7.10(m, 4H), 8.45(dd, 1H, J=12.6), 11.47(d, J=14.6), 12.48(d, J=14.6)
j	1.42(s, 3H), 2.77(m, 4H), 3.95(s, 3H), 5.88(s, 2H), 6.70(m, 3H), 7.10(m, 4H), 8.59(dd, 1H, J=12.6), 11.79(d, J=14.6), 12.66(d, J=14.6)
k	1.43(s, 3H), 2.36(s, 3H), 2.88(m, 4H), 5.85(s, 2H), 6.70(m, 3H), 7.22(m, 4H), 8.48(dd, 1H, J=12.0), 11.66(d, J=14.0), 12.63(d, J=14.0)
l	1.43(s, 3H), 2.41(s, 6H), 2.76(m, 4H), 5.99(s, 2H), 6.77(m, 3H), 7.20(m, 3H), 8.10(dd, 1H, J=11.6), 11.01(d, J=14.0), 11.98(d, J=14.0)
m	1.13(m, 5H), 1.31(s, 3H), 2.54(m, 4H), 5.96(s, 2H), 6.76(m, 3H), 7.18(m, 3H), 7.85(dd, 1H, J= 11.6), 10.91(d, 14.6), 11.82(d, J=14.6)

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Received 25 March, 2002