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5-ARYL-3-METHYL-2-CYCLOHEXEN-1-ONES FROM 4-ARYL-1, 4-DIHYDROPYRIDINES (HANTZSCH ESTERS)

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Abstract. Reductive cyclization of 2,6-dimethyl-3,5-dicarboxyethyl-4-aryl-1,4-dihydropyridines using sodium and methanol as solvent produces the 5-aryl-3-methyl-2-cyclohexen-1-ones.

The rigid analogue approach is a powerful tool for the medicinal chemist for clarifying the structural and conformational requirements for receptor selectivity.[1] A rigid analogue is a blocked conformation of the conformationally lead; the chemical manipulation of the molecule which is necessary to reduce its flexibility should be done in such way that no other physicochemical properties are substantially altered apart from conformation. Loperamide **1** is an antidiarrheal agent. It is 50 times more potent than codeine.[2] As a part of our program on drug design[3] we tried to synthesized conformationally restricted analogues of **1** and required workable amounts of piperidines as such **2**. Reaction of 1,4-

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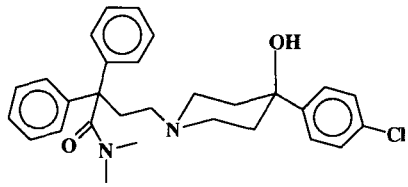
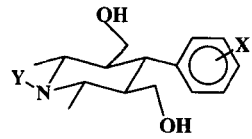


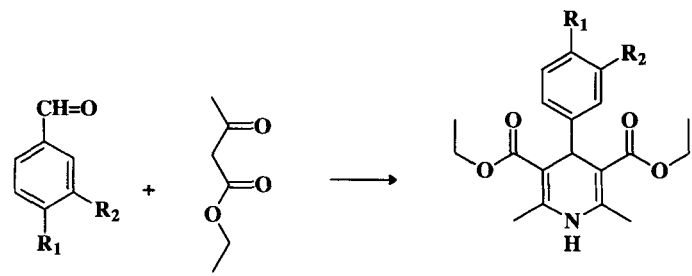
1



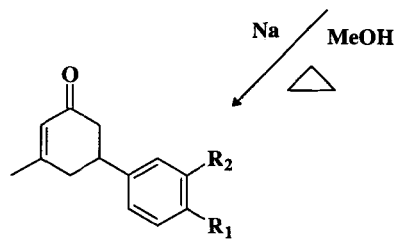
2

dihydropyridines or pyridines with sodium and ethanol to give piperidines is a well-known process.[4]

However, during the treatment of 1,4-dihydropyridines **3a** with sodium and methanol we observed the unusual transformation of **3a** to give **4a** in 80% yield. This prompted us to investigate the behavior of other 1,4-dihydropyridines (**3b-h**)



3a-h



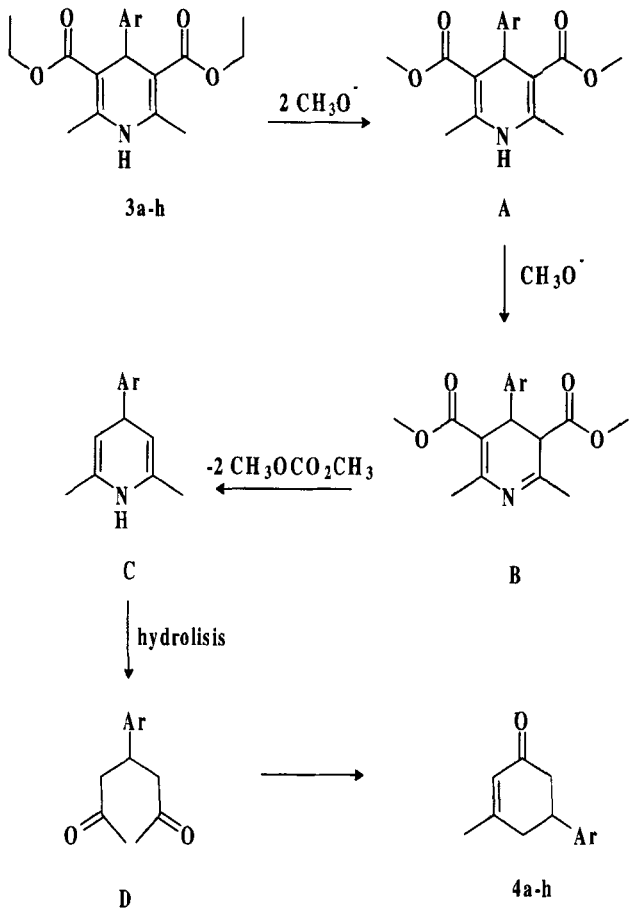
4a-h

TABLE 1. Yields and Physical Data for Compounds **4**

Compound No	R_1	R_2	Reaction time(h)	Yield [%]	m.p. °C (lit.)	IR cm^{-1}
4a	CH_3	H	3.2	80	oil	1665
4b	OCH_3	H	4.0	30	56-58 (57-60[10])	1662
4c	H	H	2.0	25	oil (ref.[8])	1662
4d	H	OC_6H_5	2.5	25	112-13	1659
4e	Br	H	3.0	49	65-66	1658
4f	Cl	H	5.0	25	54-55 (54-55[9])	1661
4g	OH	OCH_3	6.0	30	oil	1657
4h	OH	H	4.0	34	108-109 (106-108[10])	1654

[a] All the new products gave satisfactory C,H analysis.

under sodium in methanol conditions, and in all the cases the corresponding 3-methyl-5-phenyl-2-cyclohexen-1-ones (**4b-h**) were obtained in varying amounts. The formation of (**4a-h**) from (**3a-h**) in the presence of sodium and methanol can be rationalized as shown below. Compounds (**3a-h**) react with two moles of sodium methoxide to yield the transesterification intermediate **A** which suffers a deconjugation, favored by the presence of the base, to produces **B**. This could undergo a double decarbomethoxylation to give **C**. Hydrolysis of **C** gives diketone



intermediate **D**; the closure of **D** toward the 2-cyclohexenone ring produces the final products (**4a-h**). In spite that our study was synthetically oriented from its beginning we tried to detect some intermediates by ^{13}C NMR experiments to support this plausible mechanism, however we only could detect the transesterification intermediate **A**.

A related methodology has been used for the synthesis of cyclohexenones from pyridines by the Birch reduction (sodium-ammonia followed by refluxing with

acid) with poor yields.[5] Danishefsky applied this procedure to the synthesis of homo-oestrone utilizing aqueous sodium hydroxide as hydrolytic agent[6] and Kamikawaji also has been described the acid transformation of a calcium antagonist 1,4-dihydropyridine into a cyclohexenone ring.[7] The method described here has advantage over the above ones because the preparation of pyridines, usually prepared by oxidation of dihydropyridines, is avoided and the reaction times are short.

Experimental

All melting points are uncorrected. The IR spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were determined on a Varian FT-200 and Varian FT-300 instrument. All NMR spectra were obtained with the pulse sequence as part of the spectrometer's software and was determined in $CDCl_3$ solution containing $SiMe_4$ as the internal standard with chemical shifts (δ) expressed downfield from $SiMe_4$. Mass spectra were recorded using Jeol SX-102 mass spectrometer using the direct inlet system with an ionization energy of 70 eV, an emission current of 100 μA and ion source temperature of 150 °C. Column chromatography was carried out on Merck Kieselgel 60 F_{254}. Thin layer chromatography was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agent.

2,6-Dimethyl-3,5-diethoxycarbonyl-4-(substituted-phenyl)-1,4-dihydropyridines **3a-h** have been prepared following reported procedures.[11] The structures of compounds **3a-h** were supported by ir, ^{1}H-nmr and mass spectral data which are

similar to those reported.[12, 13, 14, 15, 16] Compound **3d** is new and its physical and spectroscopic data is below.

2,6-Dimethyl-3,5-diethoxycarbonyl-4-(3-phenoxyphenyl)-1,4-dihydropyridine, **3d**

This compound was obtained as colorless solid (50%), 148-149°C, ir ($CHCl_3$): 3343 (NH), 1698(CO) cm^{-1}; ^1H nmr: δ 1.18 (t, J= 7.3 Hz, 6H, 2 x CH_3-CH_2), 2.31 (s, 6H, 2 x CH_3-C2, C6), 4.07 (q, J= 7.3 Hz, 4H, 2 x -CH_2-O-), 4.96 (s, 1H, H4), 5.67 (bs, 1H, NH), 7.0-7.3 (m, 4H, Ar-H); ms: M^+ at m/z 421. Analysis Calc. for $C_{25}H_{27}O_5N$; C, 71.24; H, 6.46; Found.; C, 71.29; H, 6.45.

The structures of compounds **4b, c, f** and **h** were supported by ir, ^1H-nmr and mass spectral data which are similar to those reported.[10, 8, 9, 10] Compound **4a, d, e** and **g** are new and their physical and spectroscopic data are below.

Preparation of 3-Methyl-5-(4-methylphenyl)-2-cyclohexen-1-one (**4a**)

Typical Procedure (R_1=H; R_2= CH_3)

0.308 g of sodium (14.4 x 10^{-3} mol) were added portionwise over a period of 2 h to a solution of 0.3 g of **3a** (1.2 mmol) in 2 mL of anhydrous methanol under nitrogen atmosphere. The mixture was refluxed for 3.2 h and then added 2.5 mL of water. The resulting solution was extracted with methylene chloride (25 mL x 3). The extract was dried (sodium sulphate) and concentrated to leave a residue which was column chromatographed (silica gel). Elution with hexane/ ethyl acetate, 90/10, afforded **4a** as an oil (0.0287 g, 80 %); ^1H-nmr: δ 2.01 (s, 3H, CH_3-C3), 2.4-2.7 (m, 4H, H-4, H-6), 3.2-3.4 (m, 1H, H-5), 5.98(bs, 1H, H-2) 7.1-7.2 (m, 4H, Ar.); ms: m/z 200 (M+), Anal. Calc. for $C_{14}H_{16}O$: C, 81.99; H, 6.52.Found: C, 82.10; H, 6.50.

3-Methyl-5-(3-phenoxyphenyl)-2-cyclohexen-1-one (**4d**)

Colorless solid, mp 112-113; ^{1}H-nmr: δ 1.99 (s, 3H, CH_3-C3), 2.4-2.7 (m, 4H, H-4, H-6), 3.2-3.4 (m, 1H, H-5), 5.96 (bs, 1H, H-2), 7.3-7.4 (m, 4H, Ar.); ms: m/z 278 (M+), Anal. Calc. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52.Found: C, 82.10; H, 6.50.

3-Methyl-5-(4-bromophenyl)-2-cyclohexen-1-one (**4e**)

Colorless solid, mp 65-66 °C; ^{1}H-nmr: δ 2.0 (s, 3H, CH_3-C3), 2.4-2.7 (m, 4H, H-4, H-6), 3.2-3.4 (m, 1H, H-5), 5.98 (bs, 1H, H-2), 7.48 (dd, J= 8.2 Hz, H2', H6'), 7.10 (dd, J= 8.2 Hz, 2H, H3', H5'); ms: m/z 264 (M+), Anal. Calc. for $C_{13}H_{16}OBr$: C, 58.89; H, 4.94. Found: C, 58.92; H, 4.98.

3-Methyl-5-(4-hydroxy-3-methoxyphenyl)-2-cyclohexen-1-one (**4g**)

Oil; ^{1}H-nmr: δ 1.98 (s, 3H, CH_3-C3), 2.5-2.6 (m, 4H, H-4, H-6), 3.1-3.3 (m, 1H, H-5), 3.87 (s, 3H, OCH_3), 5.52 (bs, 1H, -OH), 5.94 (bs, 1H, H-2), 6.7-6.9 (m, 3H, Ar-H.); ms: m/z 232 (M+), Anal. Calc. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.41; H, 6.96.

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