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An efficient and green protocol for the preparation of cycloalkanols: a practical synthesis of venlafaxine

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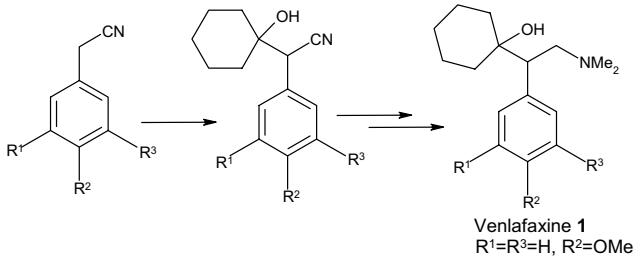
Abstract—The condensation of arylacetonitriles with cyclic ketones using aqueous NaOH or KOH under phase transfer catalysis gives almost quantitative yields of cycloalkanols. This protocol is utilized for a practical synthesis of the antidepression drug, venlafaxine.

1. Introduction

Venlafaxine[1,2] **1** is a new generation antidepression drug, quite different from other antidepressants having a unique structure and morphological effects. The earlier patented methods for its synthesis involve the use of strong bases such as *n*-BuLi,[3,4] LDA,[5] NaOMe, NaOEt, $NaNH_2$, NaH,[6] etc., for coupling *p*-methoxyphenylacetonitrile **2** with cyclohexanone **3** under anhydrous conditions, at −78 °C, to give the 1-[cyano(4-methoxyphenyl)methyl]cycloalkanol **4**. The yields under these conditions are low and are not ideally suited to large scale industrial synthesis.

2. Results and discussion

Our interest in developing mild and green protocols[7a,b,f–r] led us to undertake a practical and efficient synthesis of this commercially important drug. Cycloalkanols serve as important intermediates for the synthesis of potent drugs like venlafaxine. In pursuit of methods for forming C–C bonds and functional group transformations under aqueous conditions[7f–r] we have developed a very mild, general and efficient method for the synthesis of such cycloalkanols (see Scheme 1). Our protocol employs simple bases such as NaOH and KOH in an aqueous medium under phase transfer conditions. In addition, this protocol can be successfully employed for the synthesis of a wide variety of other natural products[7h] and commercially important pharmaceuticals.[7i]



Scheme 1.

Thus, the condensation of *p*-methoxyphenylacetonitrile **2** with cyclohexanone **3** was carried out using 10% aqueous NaOH or KOH in the presence of tetrabutylammonium hydrogen sulfate ($TBAHSO_4$) as phase transfer catalyst at 0–15 °C to give almost quantitative yields of 1-[cyano(4-methoxyphenyl)methyl]cycloalkanol **4** within 30 min–1 h. The product precipitated from the aqueous medium, and was filtered off to obtain the pure product. The reaction could also be carried out using powdered NaOH or KOH, at 0–15 °C without a phase transfer catalyst to furnish **4** in 87% yield within 30 min. The reaction can also be performed using polyethylene glycol (MW-6000) as the phase transfer catalyst when yields of up to 73% were obtained, albeit in 48 h. Thus, the process eliminates the use of organic solvents

Keywords: Condensation; Cycloalkanols; Phase transfer catalyst.
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Table 1.

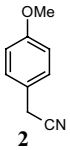
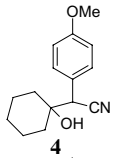
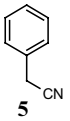
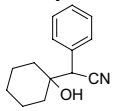
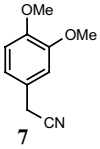
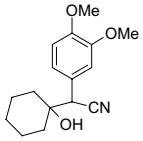
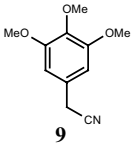
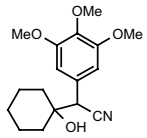
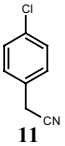
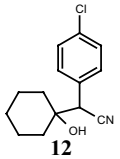
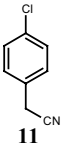
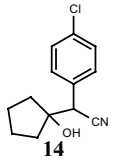
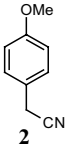
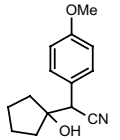
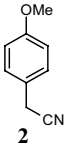
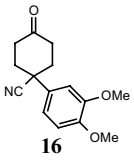
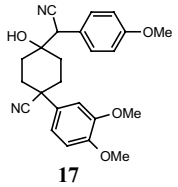
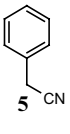
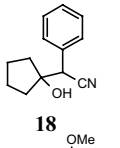
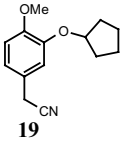
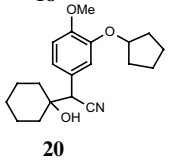
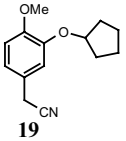
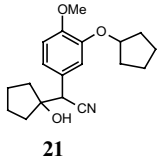
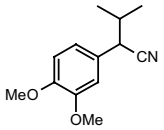
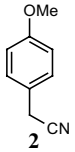
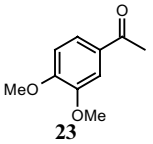
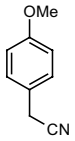
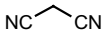
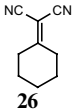
Entry	Nitrile	Ketone	Product	PTC[a]	Time	%Yield
1	 **2**	 **3**	 **4**	$TBAHSO_4$	1 h	97
2	 **5**	 **3**	 **6**	$TBAHSO_4$	1 h	87
3	 **7**	 **3**	 **8**	$TBAHSO_4$	1 h	95
4	 **9**	 **3**	 **10**	$TBAHSO_4$	1 h	90[b]
5	 **11**	 **3**	 **12**	$TBAHSO_4$	45 min	87
6	 **11**	 **13**	 **14**	$TBAHSO_4$	45 min	73[c]
7	 **2**	 **13**	 **15**	TBAI[d]	1 h	83
8	 **2**	 **16**	 **17**	$TBAHSO_4$	45 min	56[e]
9	 **5**	 **13**	 **18**	TBAI[d]	1 h	96
10	 **19**	 **3**	 **20**	TBAI[d]	2 h	66
11	 **19**	 **13**	 **21**	$TBAHSO_4$	2 h	96

Table 1 (*continued*)

Entry	Nitrile	Ketone	Product	PTC[a]	Time	%Yield
12	 **22**	 **3**	NR[f]	$TBAHSO_4$	Overnight	—
13	 **2**	 **23**	NR[f]	$TBAHSO_4$	Overnight	—
14	 **2**	 **24**	NR[f]	$TBAHSO_4$	Overnight	—
15	 **25**	 **3**	 **26**	$TBAHSO_4$	30 min	77

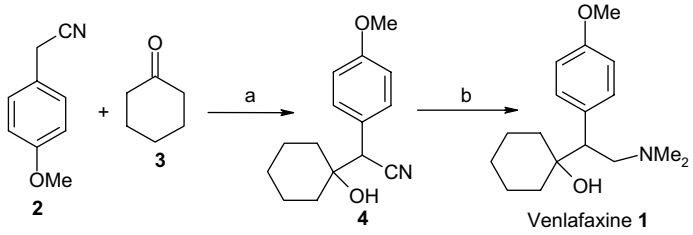
[a] PTC = phase transfer catalyst.
[b] Powdered nitrile was used.
[c] About 10% dehydrated product was obtained.
[d] TBAI = tetrabutylammonium iodide.
[e] Powdered ketone was used.
[f] No reaction observed even at room temperature.

either as the reaction medium or in the workup (extraction), employing water as the reaction medium, thereby making it a simpler, cleaner and 'greener' process. In order to generalize this reaction, a wide variety of arylacetonitriles were treated with different ketones. The results are listed in Table 1.

From the table it is evident that a wide variety of arylacetonitriles undergo C–C bond formation with cyclic ketones to give good to excellent yields of the corresponding cycloalkanols. Both cyclohexanone as well as cyclopentanone were shown to react efficiently under these conditions. An α-substituted arylacetonitrile (entry 12) however, did not react with cyclohexanone under these conditions. Aromatic and acyclic ketones (entries 13 and 14) also failed to undergo the reaction. Even malononitrile (entry 15) was shown to undergo facile C–C bond formation with cyclohexanone. However, it was found that when the reaction is carried out at room temperature, the corresponding dehydrated product was formed inevitably, over the same period of time, exclusively!

Having developed a mild protocol for the condensation of arylacetonitriles with ketones, the key intermediate **4** was synthesized in an almost quantitative yields. The second step in the patent[3] involves the use of the expensive catalyst, Rh/Al_2O_3. Further simplifying the process, reduction of the nitrile to venlafaxine was performed under a hydrogen atmosphere (200 psi) using Raney nickel as the catalyst in the presence of formalin[7b] to furnish venlafaxine **1**. This novel procedure for reduction of a nitrile to an amine and subsequent *N*,*N*-dimethylation was performed in one-pot (Scheme 2).

Although, the yield of this reaction is 30%, 60% of the starting material was recovered and could be recycled which becomes attractive from an industrial point of view. Thus, in the second step, the expensive catalyst was replaced by a cheaper catalyst viz Raney nickel.



Scheme 2. Reagents and conditions: (a) 10% aqueous NaOH, $TBAHSO_4$, 0–15 °C, 30 min–1 h, quantitative yield; (b) H_2, 280 psi, formalin, MeOH, 100 °C, 30% (60% cycloalkanol is recovered).

Alternatively, cycloalkanol **4** could be reduced with $LiAlH_4/AlCl_3$ to give the corresponding amine (quantitative yield), which could be further *N*,*N*-dimethylated using formalin and formic acid in the presence of a large excess of water[8] to furnish **1** (85–90% yield). Thus, novel conditions were developed where water is used as the reaction medium and mild, readily and cheaply available bases are employed in the key step. The use of an expensive catalyst was avoided and the reaction could be performed employing a cheaper catalyst instead.

The hydrochloride salt of **1** was prepared using isopropanol saturated with HCl gas followed by recrystallization from ethyl acetate.

3. Conclusion

In conclusion, we have developed a novel protocol for the condensation of arylacetonitriles with cyclic ketones in an aqueous medium and utilized it for the synthesis of the commercially important drug, venlafaxine. The process is simple to operate, and eliminates cumbersome purification techniques such as column chromatography, making it very attractive from a commercial point of view.

4. Experimental

4.1. A typical procedure for the preparation of cycloalkanols

1-[Cyano(4-methoxyphenyl)methyl]cycloalkanol (**4**): An ice-cooled mixture of *p*-methoxyphenylacetonitrile (100 g, 0.680 mol), 10% aq NaOH soln (100 mL, 0.250 mol) and tetrabutylammonium hydrogen sulfate (5 g, 0.014 mol) was stirred for 30 min. A dark red colour was observed due to the anion. To this was added cyclohexanone (67 g, 0.680 mol) in small portions, at 0 °C, with vigorous stirring, such that the temperature did not rise above 15 °C. After 30 min–1 h, a white solid formed. The solid was crushed and the reaction mixture was again stirred vigorously at room temperature for a further 1 h. The solid was filtered, washed with water until neutral to pH paper and dried. Crystallization from ethyl acetate–petroleum ether (500:350, v/v) gave a bright white solid (161.66 g, 97%; mp 125–126 °C, lit.[3] mp 125–127 °C).

4.2. Reduction of the nitrile

2-[Dimethylamino(4-methoxyphenyl)ethyl]cyclohexanol (**1**): To a solution of cycloalkanol **4** (5 g, 0.02 mol) in methanol (100 mL) was added formalin (35% soln, 25 mL) and Raney nickel (2.5 mL aqueous suspension, in a measuring cylinder, washed three–four times with methanol to remove water). The mixture was subjected to reduction using Raney nickel under a H_2 atmosphere (200 psi) at 60 °C, for 6 h. The reaction mixture was allowed to cool to room temperature and filtered. The catalyst was thoroughly washed with methanol (4×25 mL). The combined filtrate was concentrated under reduced pressure to afford an oily residue, which was then dissolved in ethyl acetate and partitioned between 10% aq HCl. The aqueous layer was washed with ethyl acetate, basified using 10% aq NaOH soln, saturated with NaCl, and the product extracted into ethyl acetate, washed with brine (2×25 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a bright white solid (1.69 g, 30%, mp 74–76 °C). The first ethyl acetate fraction after washing with water (2×25 mL), drying over anhydrous Na_2SO_4 and concentration under reduced pressure returned unreacted nitrile **4** (3 g, 60%). The hydrochloride salt of venlafaxine **1** was prepared using isopropanol saturated with HCl gas to give bright white crystals (mp 224–226 °C, lit.[3] mp 225–226 °C).

Acknowledgements

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