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A synthesis of trifluoromethyl-substituted naphthalenes

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Abstract

Alkyl and aryl Grignard reagents add to 1-(3,4-dihydro-*2H*-5-pyranyl)-2,2,2-trifluoro-1-ethanone by 1,4-addition, but benzyl Grignard reagents react in good yield by 1,2-addition. Dehydration of the resulting alcohols affords intermediate dienes, which readily undergo cyclisation to give substituted trifluoromethyl-naphthalenes. Addition to other trifluoromethylketones permits access to a range of novel fluorinated naphthalenes and benzenes. © 2000 Published by Elsevier Science Ltd.

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Acyclic fluorinated building blocks[1] have been used widely in the synthesis of fluorinated heterocyclic compounds. Introduction of trifluoromethyl side chain substituents into aromatic carbocycles via a building block approach permitting construction of the ring with incorporation of the trifluoromethyl substituent is little developed. The possibility that the [3+3] benzannulation procedures, recently developed by Junjappa et al.[2] and reviewed by Katritzky et al.,[3] might be used to give fluorinated naphthalenes, is attractive. In this methodology an unsaturated ketone is reacted with a benzyl organometallic reagent to afford a 1,2-adduct, which on dehydration affords aromatic products. In order that this procedure might be applied to trifluoromethyl-ketones, thus giving trifluoromethyl substituted aromatic compounds, it is essential that the benzyl organometallic reagent undergo 1,2-addition with, for example, a β-alkoxy-α,β-unsaturated ketone, rather than the possible 1,4-addition (see Scheme 1).

In the case of additions of Grignard reagents to unsaturated ketones, not having β-alkoxy- or other heteroatom substitutions, it has been recognised[4] that a charge control preferentially leads to 1,2-addition, but, in contrast, an orbital control leads preferentially to 1,4-addition. Allyl Grignards uniformly react[5] preferentially by 1,2-addition, but examples are known[6] of preferential 1,4-addition of benzyl Grignard reagents and in many examples[7] alkyl, aryl and benzyl Grignard reagents give mixtures of products. Examples have been reported by Gustafsson,[8] where benzyl magnesium halides preferentially react by 1,2- or 1,4-depending upon the nature of the halide. In the case of β-alkoxy-α,β-unsaturated methyl ketones[9] reaction with

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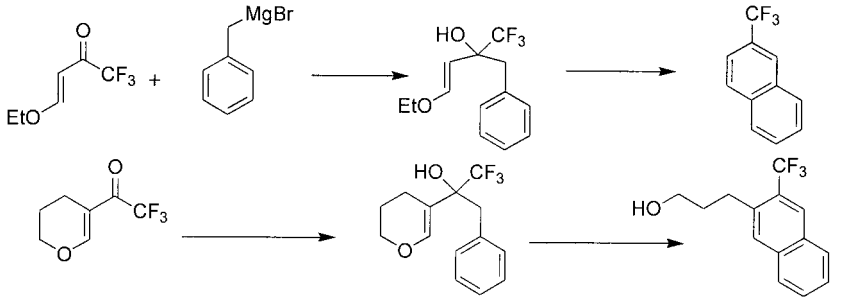
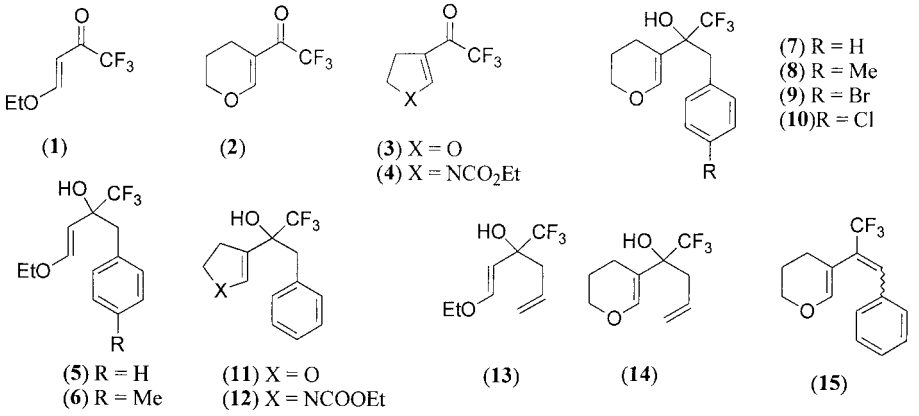


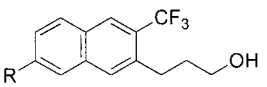
Scheme 1.

phenyl magnesium bromide gives both 1,2- and 1,4-adducts. Cases having both a β-alkoxy-substituent and trifluoromethyl-substitution have been little examined. With the β-alkoxy-α,β-unsaturated trifluoromethyl ketone (**1**)[10] aryl magnesium bromides undergo 1,4-addition. We establish in this paper that, in contrast to alkyl and aryl Grignard reagents, which preferentially undergo 1,4-addition, reaction with benzyl Grignard reagents occurs by 1,2-addition, thus enabling us to synthesise a range of substituted trifluoromethylnaphthalenes.

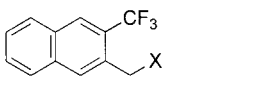


The required acyclic and cyclic β-alkoxy-α,β-unsaturated trifluoromethyl ketones (**1**–**3**)[11] are readily available and a β-amino analogue **4**,[12] prepared from proline, has recently been described. Reactions of both the acyclic ketone **1** and the cyclic ketone **2** with phenyl magnesium bromide and alkyl magnesium bromides give mainly products of 1,4-addition; e.g. phenyl magnesium bromide and octyl magnesium bromide give by 1,4-addition with the ketone **2** *cis*-products in 79 and 67% yields, respectively. Similarly, ketone **1** reacts[10] with phenyl magnesium bromide via 1,4-addition, but not 1,2-addition. In sharp contrast we find that benzyl magnesium bromides give 1,2-adducts with the cyclic ketone **2** in satisfactory yields[13] (see Table 1). The structures of the 1,2-adducts are established by observation of the signal of the vinylic proton at about δ 6.5 ppm and the OH absorption at 3450 cm^{-1}. A structural confirmation was obtained[14] by a single crystal X-ray analysis of the adduct **9**, prepared from ketone **2**. Similarly, benzyl magnesium halides preferentially undergo 1,2-addition to the acyclic ketone **1**, the cyclic ketone **3** and the pyrrole analogue **4** affording the alcohols (**5**, **6**, **11** and **12**). The spectroscopic data obtained for all the alcohols (**5**–**12**) reported in Table 1 are in good agreement with data obtained for the alcohol **9**. These additions establish that a route to trifluoromethylnaphthalenes can be based on

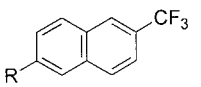
Table 1



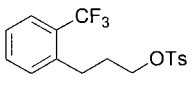
(**16**) R = H
(**17**) R = Me
(**18**) R = Br
(**19**) R = Cl



(**20**) X = CH_2OH
(**21**) X = CH_2NHCO_2Et
(**25**) X = CH_2CO_2H
(**26**) X = CO_2H



(**22**) R = H
(**23**) R = Me



(**24**)

Ketone	Grignard Reagent	Alcohol	(Yield %)	Aromatic	(Yield %)
(**1**)	$PhCH_2MgBr$	(**5**)	55	(**22**)	84
(**1**)	*p*-$MeC_6H_4CH_2MgBr$	(**6**)	45	(**23**)	95
(**2**)	$PhCH_2MgBr$	(**7**)	93	(**16**)	82
(**2**)	*p*-$MeC_6H_4CH_2MgBr$	(**8**)	97	(**17**)	90
(**2**)	*p*-$BrC_6H_4CH_2MgBr$	(**9**)	74	(**18**)	92
(**2**)	*p*-$ClC_6H_4CH_2MgBr$	(**10**)	80	(**19**)	94
(**3**)	$PhCH_2MgBr$	(**11**)	34	(**20**)	92
(**4**)	$PhCH_2MgBr$	(**12**)	25	(**21**)	63
(**2**)	$CH_2CH{=}CHMgBr$	(**14**)	82	(**24**)	60

a preferred 1,2-addition of benzyl Grignards to cyclic α,β-unsaturated trifluoromethyl ketones, having β-heteroatom substituents. Allyl magnesium bromide also adds to the ketones **1** and **2** by 1,2-addition, giving the alcohols **13** and **14** and crotyl magnesium bromide and cinnamyl magnesium bromide add to the ketones **1** and **2** by 1,2-addition.

An effective procedure for dehydration affording naphthalenes was established using *p*-toluenesulphonic acid in toluene as the catalyst. Under mild conditions dehydration of adduct **7** gave the dienes **15** in 84% yield. Under more vigorous conditions the adduct **7** gave the naphthalene **16** in 82% yield. Under similar conditions the dienes **15** gave the naphthalene **16**. Adducts from the cyclic ketones **2** and **3** gave the alcohols (**17**–**20**) in good yield (see Table 1). Similarly, dehydration of alcohol **12** gave the naphthalene **21** having an amide side-chain in 63% yield. The procedure is also effective with adducts derived from the acyclic ketone **1**. Dehydration of the adducts **5** and **6** afforded the known 2-trifluoromethylnaphthalene[15] **22** and 2-methyl-6-trifluoromethylnaphthalene **23**, respectively. Reaction of the adduct **14** under similar conditions, but for a longer period, gave the tosylate **24**.

The major significance of these results is the development of a regiospecific route to 2-trifluoromethyl benzenes and naphthalenes. 3,6-Disubstituted 2-trifluoromethyl-naphthalenes have not been prepared prior to our work. The interest in the side-chain alcohols is enhanced by their possible transformation to other substituents, thus offering a wider range of aromatic end-groups. The point is illustrated by oxidation using Jones' reagent of the alcohols **16** and **20** to the naphthyl-propionic and acetic acids **25** (90%) and **26** (85%), respectively. 3-Substituted-2-trifluoromethylnaphthalenes have already been prepared[16] in a study of candidate drugs to be used against diabetes. Our access to a series of trifluoromethyl-substituted naphthalenes carrying additional alcohol, acid and amine end-groups promises much scope for structural elaboration.

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