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A Stereoselective Synthesis of Tri-substituted Alkenes. The Nickel-Catalysed Coupling of Grignard Reagents with 6-Alkyl-3,4-dihydro-2H-pyrans.

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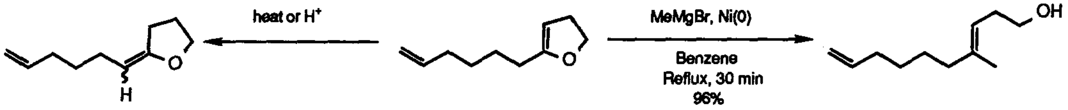
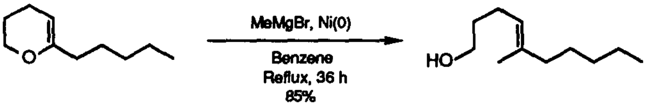
Abstract. *The nickel-catalysed coupling of certain Grignard reagents with 6-alkyl-3,4-dihydro-2H-pyrans is highly stereoselective and gives tri-substituted alkenes with retention of configuration. The method was applied to the synthesis of (E)-3-Acetoxy-7-methyl-6-nonene, the aggregation phermone of the square-necked grain beetle.*

5-Alkyl-2,3-dihydrofurans react with Grignard reagents in the presence of Ni(0) catalysts to give homoallylic alcohols (Wenkert reaction)[1,2]. The reaction is clean, efficient, easy to do on a 100 mmol scale, and highly stereoselective as exemplified by the preparation of (**2**)[3]. There is one minor detraction to the method: the dihydrofurans are sensitive to mild acid or prolonged heating and rearrange to the more thermodynamically stable exocyclic isomers (e.g. **3**)[4]. Since these too undergo Ni(0)-catalysed coupling with Grignard reagents[5], their presence can lead to mixtures of alcohols which are difficult to separate.



(3) (1) (2)

We now report the results of a study of the scope and stereochemistry of the Wenkert reaction on 6-alkyl-3,4-dihydro-2H-pyrans. As substrates in the coupling, the dihydropyrans have two advantages: they are generally easier to prepare than the dihydrofurans[6] and they are more stable to heat and mild acid since the double bond is more thermodynamically stable in the endocyclic position[7]. However, the dihydropyrans are also much less reactive requiring 24-48 h for the reaction to go to completion compared with less than 30 min for the corresponding dihydrofurans. The general procedure is illustrated by the preparation of (**5**).



(4) (5)

To a magnetically stirred suspension of $(PPh_3)_2NiCl_2$ (0.1 mmol) in dry benzene (5 ml) was added at ambient temperature 0.2 mmol of 3M MeMgBr in ether under nitrogen. The resultant red solution was stirred for 15 min whereupon 3M MeMgBr (2 ml, 6 mmol) in ether was added and the solvent removed *in vacuo* and the nitrogen atmosphere restored. To the resultant dark sludge benzene (5 ml) was added followed by a solution of the dihydropyran (**4**)(308 mg, 2 mmol) in benzene (2 ml). The black reaction mixture was then refluxed under nitrogen. After 2, 4, and 8 h further aliquots (0.06 mmol each) of catalyst were added and refluxing continued (*ca* 36 h total) until the reaction was complete. The reaction mixture was poured into NH_4Cl/NH_3 and stirred for 1h. After the usual extractive work-up the product was purified by chromatography on silica gel (hexane; ether-hexane) to remove biphenyl, unreacted dihydropyran, and polar impurities. Distillation *via* Kugelrohr gave (**5**) (289 mg, 1.7 mmol, 85%) as a colourless oil. The product was at least 97% (E) by 360 MHz nmr spectroscopy. Further examples of the Wenkert reaction using dihydropyrans are given in the Table.

The diminished reactivity of the dihydropyrans imposes a number of limitations on the scope of the reaction:

(1) Under prolonged refluxing in benzene, the catalyst is gradually destroyed[8] and must be replenished at intervals. Whereas the coupling with dihydrofurans requires as little as 1 mol%, the dihydropyrans require 5 mol% initially followed by 3-4 further increments of 3 mol% and even then small amounts (*ca* 10%) of dihydropyran remain.

(2) Owing to gradual decomposition of the dihydropyrans under the reaction conditions, the yields are seldom better than 50-60%.

(3) Unlike the dihydrofurans, the coupling is restricted to Grignard reagents lacking β-hydrogens[9].

(4) 5,6-Dialkyl-substituted-3,4-dihydro-2H-pyrans (*e.g.* **21**) react stereoselectively to give tetra-substituted alkenes but only in poor yield.

Various attempts to circumvent these limitations have not been successful. For example, addition of $ZnCl_2$ or BF_3-Et_2O and sonication failed to yield improvements in yield or rate as did variation of the solvent or the phosphine ligands on the catalyst.

A 4-step synthesis of the aggregation pheromone (**26**)[10] of the square-necked grain beetle *Cathartus quadricollis* illustrates the synthetic potential of the method. The key step of the sequence, the Ni(0)-catalysed coupling of MeMgBr with 2,6-diethyl-3,4-dihydro-2H-dihydropyran (**24**) gave the alcohol (**25**) in 55% yield (>97% E).

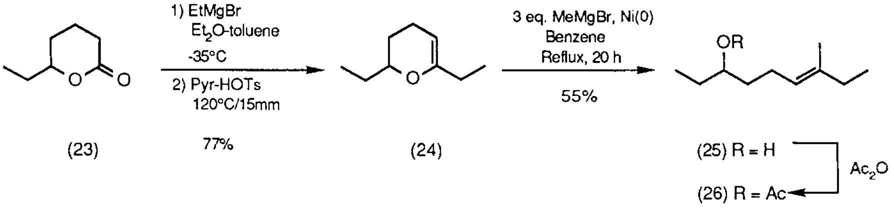
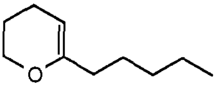
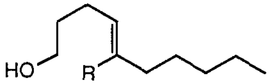
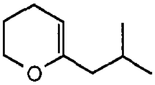
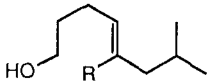
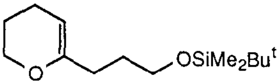
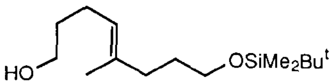
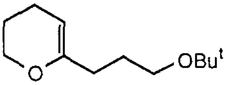
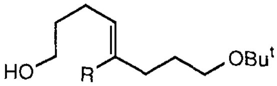
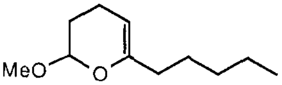
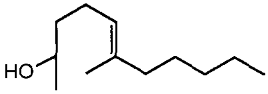
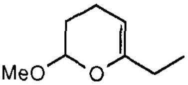
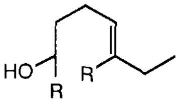
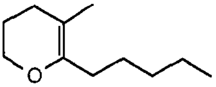
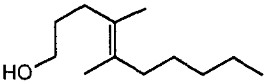


TABLE. Products from the Ni(0)-Catalysed Coupling of Grignard Reagents with Dihydropyrans

Dihydropyran*	Grignard Reagent	Product (Yield %)*
 (4)	PhMgBr Me_3SiCH_2MgCl	 (6) R = Ph (70%) (7) R = CH_2SiMe_3 (54%)
 (8)	MeMgBr PhMgBr	 (9) R = Me (39%) (10) R = Ph (49%)
 (11)	MeMgBr	 (12) (45%)
 (13)	MeMgBr PhMgBr	 (14) R = Me (56%) (15) R = Ph (63%)
 (16)	MeMgBr	 (17) (35%)
 (18)	MeMgBr PhMgBr	 (19) R = Me (35%) (20) R = Ph (56%)
 (21)	MeMgBr	 (22) (4%)

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* All compounds were characterised by IR, ^1H and ^{13}C NMR, and high resolution MS including accurate mass.

CONCLUSION: Dihydropyrans undergo Ni(0)-catalysed coupling with Grignard reagents but they are much less reactive than the corresponding dihydrofurans. However with Grignard reagents lacking ß-hydrogens, the coupling with dihydropyrans provides a stereoselective route to tri-substituted alkenes.

Acknowledgements We thank Dr. Richard Whitby for expert assistance and Pfizer Central Research (U.K.) for generous financial assistance.

References and Notes.

1. (a) E. Wenkert, E.L. Michelotti, C.S. Swindell, and M. Tingoli, *J. Org. Chem.*, 1984, **49**, 4894; (b) E. Wenkert, V. F. Ferreira, E.L. Michelotti, and M. Tingoli, *J. Org. Chem.*, 1985, **50**, 719.

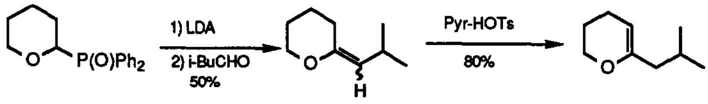
2. S. Wadman, R. Whitby, C. Yeates, P. Kocieński, and K. Cooper, *J. Chem. Soc., Chem. Commun.*, 1987, 241.

3. R. Whitby, C. Yeates, P. Kocieński, and G. Costello, *J. Chem. Soc., Chem. Commun.*, 1987, 429.

4. E. Taskinen, *Acta Chem. Scand.*, 1974, **B28**, 1234.

5. P. Kocieński and N.J.Dixon, unpublished results.

6. The dihydropyrans (**4**), (**11**), (**13**), (**16**), (**18**), and (**21**) were prepared by the alkylation of the corresponding 6-lithio-2,3-dihydro-2H-pyrans with the approprate *n*-alkyl iodides in THF according to the method of R.K. Boeckman and K.J. Bruza, *Tetrahedron*, 1981, **37**, 3997. The dihydropyran (**8**) was prepared by the acid-catalysed isomerisation of (**28**) prepared from (**27**) by the method of Ley and co-workers: S.V. Ley, B. Lygo, H.M. Organ, and A. Wonnacott, *Tetrahedron*, 1985, **41**, 3825.



(27) (28) (8)

7. E. Taskinen, *Tetrahedron*, 1978, **34**, 433.

8. By following the reaction by gas chromatography we found that coupling was rapid for *ca.* 2 h after which there was a marked decrease in rate. The rate then increased on addition of more catalyst but it was not restored to its initial value.

9. The lower reactivity of Grignard reagents with ß-hydrogens is also observed in the dihydrofurans. Whereas MeMgBr and PhMgBr react with dihydrofurans in less than 30 min, EtMgBr and *n*-BuMgBr require *ca.* 20 h for complete reaction (see reference 1c).

10. For an alternative synthesis see B.D. Johnston and A.C. Oehlschlager, *J. Org. Chem.*, 1986, **51**, 760.

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