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Regioselective Ni(II)-Assisted Alkylation of 2-Methoxy-5,6-dihydro-2H-pyran: a New Route to 2-*n*.Alkyl-5,6-dihydro-2H-pyrans

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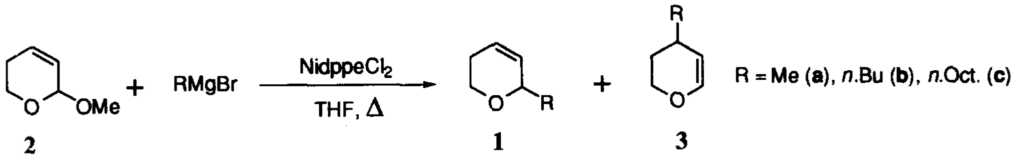
Abstract: In the presence of a catalytic amount of $NidppeCl_2$, 2-methoxy-5,6-dihydro-2H-pyran reacts with primary Grignard reagents to give the corresponding 2-*n*.alkyl-5,6-dihydro-2H-pyrans in satisfactory yields. © 1998 Elsevier Science Ltd. All rights reserved.

Owing to our interest towards the asymmetrical functionalization of prochiral cyclic allylethers, the preparation of 2-*n*.alkyl-5,6-dihydro-2H-pyrans [**1**, R=Me (**a**), *n*.Bu (**b**), *n*.Oct (**c**)] had to be carried out. Although some more or less general synthetic approaches to **1a** had been reported,[1] we deemed the protocol illustrated by Quelet and D'Angelo[2] for the preparation of **1b** particularly attractive since it could provide ready access to pyrans **1a-c** from 2-methoxy-5,6-dihydro-2H-pyran (**2**)[3] and suitable Grignard reagents. However, in those reaction conditions (2-ethoxy-5,6-dihydro-2H-pyran and *n*.BuMgBr in toluene at 80-90°C),[2] the formation of 5-ethoxynon-3-enol, arising from alkylation and ring opening, affected the overall yield. This report describes the influence of Nickel-[1,2-bis(diphenylphosphino)ethane]dichloride ($NidppeCl_2$) on the regio- and chemoselectivity of the reaction of **2** with Grignard reagents (Scheme). In undertaking this investigation, we were conscious that in the presence of a catalytic amount of CuBr organomagnesium compounds react with **2** through an allylic (C_4) substitution to afford 4-alkyl-5,6-dihydro-4H-pyrans (**3**).[5] Nonetheless, the use of ($NidppeCl_2$) as the catalyst in the reaction was not expected to alter the intrinsic (C_2) regioselectivity of the alkylation of **2** by the same organometallic reagents.[2] This belief was supported by the selective formation of allylic alcohols deriving from the reaction of 2-alkyl-1,3-dioxep-5-enes with Grignard reagents and $NidppeCl_2$,[6] as well as the regioselectivity observed in the Pd(0)-catalyzed alkylation of acetoxydihydropyrans with organozinc chlorides.[7] To assess the feasibility of the Ni(II)-assisted substitution of the methoxy group of **2** by Grignard reagents, preliminary reactions of **2** with MeMgBr and $NidppeCl_2$ were performed. Whereas in Et_2O no reaction occurred, a quantitative conversion of **2** in 2-methyl-5,6-dihydro-2H-pyran (**1a**) (95%) and its regioisomer **3a** (5%) was achieved in boiling THF (Table, entry 1).

Scheme



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Similarly, 2-*n*.butyl- (**1b**) and 2-*n*.octyl-5,6-dihydro-2H-pyran (**1c**) were obtained with comparable regioselectivity and yields (Table, entries 2 and 3).

Table. Reactions of **2** with Grignard Reagents in the Presence of $NidppeCl_2$.[a]

Entry	R	time(h)	T °C[d]	Conversion[b] (%)	Regioisomeric distribution[b,c] **1**[e]	**3**
1	Me (**a**)	4	80	100	95(60)	5[f]
2	*n*.Bu (**b**)	1	80	100	95(74)	5[g]
3	*n*.Oct (**c**)	1	80	100	95(74)	5[h]
4	*i*.Bu	2.5	40-80	100[i]	-	-
5	*i*.Pr	2.5	40-80	100[i]	-	-
6	*c*.Hex (**d**)	3.5	25	73[j]	73(20)	27[h]
7	1-Octynyl	5	80	-	-	-

[a] $[\mathbf{2}]/[RMgBr]/[NidppeCl_2 \cdot 10^{-2}]$= 1/1.5/1.5; [b] Capillary Glc; [c] The number in brakets are isolated yields in >97% regioisomerically pure **1**; [d] Temperature of the oil bath; [e] Ir, ^1H, ^{13}C NMR, Mass spectra and analytical data well agree with the reported structures; [f] See note 8; [g] See note 10; [h] Identified by Glc/mass; [i] The main (>90%) reaction products were 5,6-dihydro-2H- and 5,6-dihydro-4H-pyran identified by Glc/mass; [j] Reduction products (see note i) were formed in 65% (Glc) yield.

Although our synthetic aim had been accomplished, the peculiarity of the reaction prompted us to investigate any dependence on the nature of the Grignard reagent. The data reported in the Table (entries 4-6) point out that when both an α-branched primary and a secondary alkylmagnesium bromides were used the reductive removal of the methoxy group (Table, note h) was the main reaction feature. Furthermore no trasformation occurred when an acetylenic Grignard reagent was used (Table, entry 7). These limitations, however, do not overshadow the utility of this methodology which is more efficient and higher yielding than those previously described for the synthesis of 2-*n*.alkyl-5,6-dihydro-2H-pyrans [1,2] and complementary to that reported by Normant for the preparation of 4-*n*.alkyl-5,6-dihydro-4H-pyrans (**3**).[4]

General Procedure. The suitable organomagnesium bromide was added dropwise to a cold (0°C) mixture of $NidppeCl_2$ and **2** in THF $\{[\mathbf{2}]/[RMgBr]/[NidppeCl_2 \cdot 10^{-2}]=1/1.5/1.5\}$. The reaction mixture was heated at the suitable temperature until a satisfactory conversion was achieved (see Table) and then hydrolyzed with a saturated solution of NH_4Cl. Crude products were extracted into pentane and the organic phase was repeatedly washed with water to remove most of the THF and dried (Na_2SO_4). Products were purified by distillation.

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REFERENCES AND NOTES

1. Riobé, O., *Ann. Chim. Paris* **1949**, *4*, 593; Berti, G.; Catelani, G.; Ferretti, M.; Monti, L. *Tetrahedron* **1974**, *30*, 4013; Colonge, J.; Boisde, P. *Bull. Soc. Chim. France* **1956**, 824; Safarov, M. G.; Safarova, V. G. Raficov, S. R. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1977**, 1350.
2. Quelet, R.; D' Angelo, J. *Bull. Soc. Chim. France* **1967**, 3390.
3. Compound **2** was prepared according to the procedure reported for 2-ethoxy derivative.[4]
4. Woods, G. F.; Sanders, H.; *J. Am. Chem. Soc.* **1946**, *68*, 2483.
5. Gendreau, Y.; Normant, J. F. *Bull. Soc. Chim. France* **1979**, 305.
6. Menicagli, R.; Malanga, C.; Finato, B.; Lardicci, L. *Gazz. Chim. Ital.* **1989**, *119*, 69; Malanga, C.; Menicagli, R.; Lardicci, L. *Ibid.*, **1992**, *122*, 45.
7. Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812.
8. An authentic sample of **3a** was prepared according to a reported procedure.[9]
9. Parham, W. E.; Holmquist, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 913.
10. An authentic sample of **3b** was prepared according to Gendreau and Normant.[5]