CHEMISTRY LETTERS, pp. 427 - 428, 1985.

REACTION OF SPIRO[CYCLOHEXANE-1,3'-3H-INDOLE] WITH GRIGNARD REAGENTS IN THE PRESENCE OF CUPROUS CHLORIDE

Gonzalo RODRIGUEZ,* Yolanda BENITO, and Fernando TEMPRANO
Departamento de Química Orgánica, Universidad Autónoma, Canto Blanco, 28049-Madrid, Spain

Attack of MeMgI and PhMgBr in toluene on spiro[cyclohexane-1,3'-3H-indole] (**1**) in the presence of Cu_2Cl_2 gives 2'-substituted spiro[cyclohexane-1,3'-indolines] in quantitative yields. Also, attack of $PhCH_2CH_2MgBr$ on **1** in the presence of Cu_2Cl_2 afforded 2'-phenethyl, 2'-H and 2'-benzyl (or 2'-p-xylyl) derivatives in toluene (or p-xylene) as solvent.

1'-γ-(N',N'-dimethylamino)propyl derivatives of 2'-substituted spiro[cycloalkane-1,3'-indolines] are potentially antidepressant drugs.

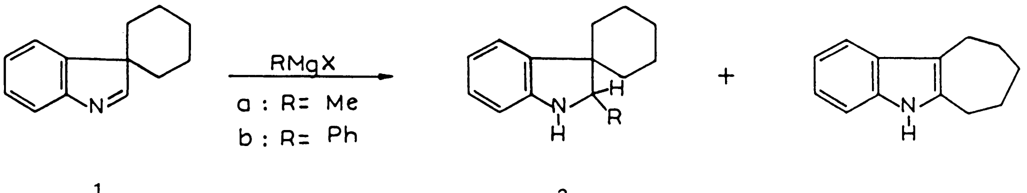
Preparation of **1** has been carried out by the Fischer reaction from cyclohexanecarbaldehyde phenylhydrazone.$^{1)}$ Nucleophilic addition of Grignard reagents on **1** was undertaken to obtain appropriate 2'-substituted spiroindolines (**2**).

Attack of MeMgI and PhMgBr on the C=N bond of **1** in ethereal solvents (diethyl ether or tetrahydrofuran) results unsuccessful and **1** was all recovered.

Organolithium reagents, with greater ionic character than the Grignard ones, exhibit the same behavior with **1** in the same ethereal solvents.

Steric hindrance affecting C=N bond of **1** by bulky pentamethylene substitution and the organometallic solvation by the ethereal solvent seems to prevent the nucleophilic addition of Grignard reagent to **1**.

To avoid the solvation effect, the reaction was carried out in toluene at 120 °C. Thus, MeMgI and PhMgBr in toluene under inert atmosphere reacted with **1** to give 39% of **2a** (picrate, mp 151-152 °C) and 5% of **2b** (picrate, mp 180-181 °C).$^{2)}$ Organolithium reagent, MeLi and PhLi, under the same experimental conditions provided 5% of **2a**, while **2b** was not detected. Moreover, those Grignard and organolithium reagents, do transform **1** to cyclohepteno[b]indole **3** (colorless crystals, mp 142-143 °C) in low extent (Table 1).



1 **2** **3**

Table 1.

Organometallic	Time/h	Yield of 2/%	Yield of 3/%
MeMgI	20	39	5
MeLi	24	5	10
PhMgBr	24	5	15
PhLi	24	-	--
MeMgI(Cu_2Cl_2)	2	100	--
PhMgBr(Cu_2Cl_2)	2	100	--

Table 2. Cu_2Cl_2 fixed as the 5.5% molar of 1

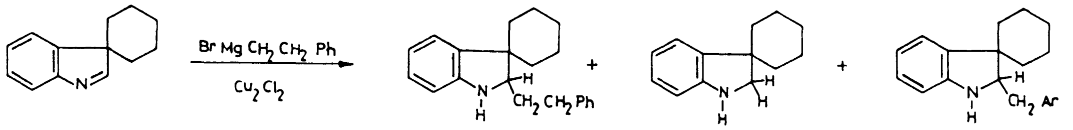
1/mol l^{-1}	MeMgI/mol l^{-1}	Yield of 2a/%	Yield of 3/%
0.1	0.1	15	presence[a]
0.5	0.5	56	presence[a]
0.05	0.1	35	--
0.25	0.5	100	--
0.01	0.01	--	100

a) Detected by GC/MS techniques.

Reaction of these Grignard reagents in toluene with 1 shows an apparently radicalic mechanism. In this way, a little amount of Cu_2Cl_2 was added to a mixture of the Grignard reagent and 1 in toluene at 120 °C. After 2-3 h, the compounds 2a and 2b respectively, were isolated in quantitative yield (Table 1). Moreover, MeLi and PhLi with 1 do not react under similar experimental conditions.

A general fact of this reaction is that is affected by: a) the molar relation of 1 to the Grignard reagent and b) dilution of this reagent in toluene. Both effects are shown at fixed reaction time (2 h) in Table 2. It is remarkable that the rearrangement product 3 is isolated in quantitative yield under dilution conditions.

Attack of $PhCH_2CH_2MgBr$ to 1 in a similar way afforded 4 (hydrochloride, mp 114-115 °C), 5 (colorless crystals, mp 76-77 °C) and 6a (colorless crystals, mp 87-89 °C). The reduction product 5 allow us to consider a radicalic intermediate from 1 on the 2'-position which incorporates hydrogen from the solvent, generating a benzyl radical as it is confirmed by the formation of 6a. A p-xylyl radical is also trapped as 6b (hydrochloride, mp 116-118 °C) when p-xylene was used as solvent.[2)]



1	SOLVENT	Yield/%	4	5	6
	Toluene		40	37	a:20 (Ar=Ph)
	p-Xylene		43	36	b:19 (Ar=p-Tolyl)

Spirocycloalkane compounds, structurally related to 1, cycloheptane and cyclooctane derivatives, gave similar results and thus, the above reactivity is independent of the steric hindrance of the cycloalkane ring as spiro substituent.

References

1) J.G. Rodríguez, Y. Benito, and F. Temprano, to be published.
2) All new compounds were fully characterized by elemental analysis and spectral data

(Received December 12, 1984)