The Journal of
Organic
Chemistry

VOLUME 57, NUMBER 17 AUGUST 14, 1992

Communications

Reactivity and Diastereoselectivity of Grignard Reagents toward the Hydrazone Functionality in Toluene Solvent

Alex Alexakis,* Nathalie Lensen, Jean-Philippe Tranchier, and Pierre Mangeney

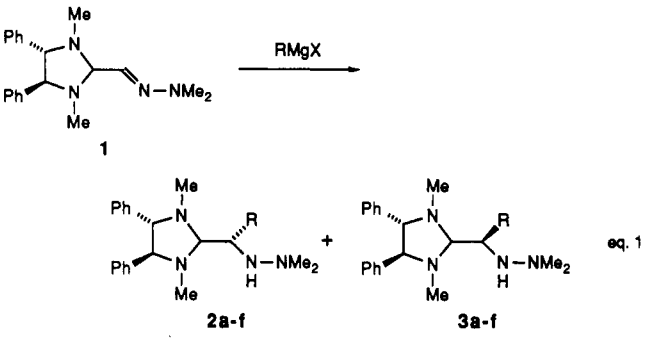
Laboratoire de Chimie des Organoéléments, URA CNRS 473, Université Pierre et Marie Curie, Tour 44-45 E2, 4 Place Jussieu, 75252 Paris Cedex 05, France

Received April 27, 1992

Summary: Grignard reagents, in toluene solvent, display a strongly increased reactivity toward the hydrazone functionality. With the chiral synthon 1, a highly diastereoselective addition occurs, through chelation control, whereas with pyrazolines **4** and **9** only the *d,l* diastereomer is formed, leading to a very short synthesis of 1,3-diphenyl-1,3-diaminopropane (**11**).

Chiral α-amino aldehydes are versatile synthons in asymmetric synthesis.[1] We recently disclosed a synthetic approach leading, efficiently, to this class of compounds.[2] This strategy is based on the use of glyoxal and a chiral diamine having a C_2 axis of symmetry, as shown in Scheme I. In the above work, the excellent diastereoselectivity (single diastereomer) is ascribed to steric control by the chiral auxiliary. Organolithium reagents in THF solvent were found to be the reagents of choice. In contrast, Grignard reagents were unreactive with chiral synthon 1 under these conditions due probably to the steric bulk of the imidazolidine moiety.[3]

We have, now, found that in less polar solvents Grignard reagents are able to react with synthon 1 (eq 1). Thus, although MeMgBr does not react at room temperature in Et_2O, it does so, quantitatively, after 24 h at reflux, affording the diastereomeric adducts **2a** and **3a** in a 20:80 ratio (see Table I, entry 2). More interestingly, the major



a : R= Me ; b : R=Pr ; c : R=Bu ; d : R=cHex ; e : R=tBu ; f : R=H ; g : R=Ph ; h=Allyl

diastereomer **3a** was the opposite of the one obtained with RLi in THF (Scheme I)! The formation of this diastereomer can be ascribed to a chelation control by the lone pair of one of the two nitrogens of the imidazolidine ring[4] and the hydrazone nitrogen (Scheme II). In such a rigid conformation, the pseudoequatorial *N*-methyl group masks the *Si* face of the hydrazone functionality. A similar model has been proposed for related systems.[5]

The higher reactivity of the hydrazone functionality may be ascribed to the Lewis acidity of the magnesium salts which increases the electrophilicity of the C=N double bond. A way to enhance both the reactivity and the diastereoselectivity is to shift to an even less polar solvent

(1) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
(2) Alexakis, A.; Lensen, N.; Mangeney, P. *Tetrahedron Lett.* **1991**, *32*, 1171.
(3) Grignard reagents are known to react with hydrazones in ethereal solvents. See among others: (a) Kharash, M. S.; Reinmuth, O. *Grignard reactions of non-metallic substances*; Prentice-Hall: New York, 1954. (b) Takahashi, H.; Tomita, K.; Otomasu, H. *J. Chem. Soc., Chem. Commun.* **1979**, 668. (c) Claremon, D. A.; Lumma, P. K.; Phillips, P. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265.
(4) It can be seen on molecular models that only the pseudoaxial nitrogen lone pair has a favorable geometry to allow such a chelation. Moreover, this pseudoaxial nitrogen lone pair should be more available since the pseudoequatorial one should better participate to an anomeric effect.
(5) (a) Ukaji, Y.; Yamamoto, K.; Fukui, M.; Fujisawa, T. *Tetrahedron Lett.* **1991**, *32*, 2919. (b) Wade, P. A.; Price, D. T.; McCauley, J. P.; Carroll, P. J. *J. Org. Chem.* **1985**, *50*, 2804.

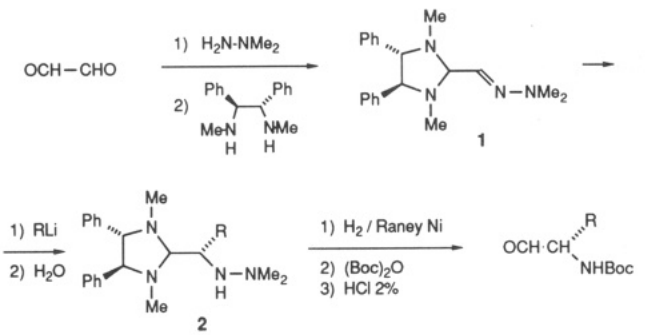
0022-3263/92/1957-4563$03.00/0

Table I. Reaction of the Chiral Synthon 1 with Various Grignard Reagents (eq 1)

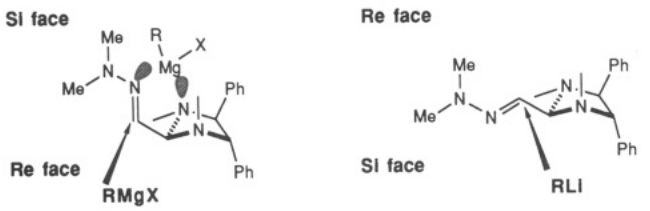
entry	RMgX	solvent	temp (°C)	time (h)	major compd	yield[a] (%)	ratio **3:2**
1	MeMgBr	THF	reflux	48			
2		Et_2O	reflux	24	**3a**	100[b]	80/20
3		toluene/Et_2O	20	1		85	94/6
4		toluene	20	1		83	94/6
5	MeMgI	toluene/Et_2O	20	1		81	94/6
6	MeMgCl	toluene/Et_2O	20	0.25		84	95/5
7	PrMgCl	toluene/Et_2O	20	1	**3b**	100[b]	100/0
8	BuMgBr	THF	reflux	48			
9		toluene/Et_2O	20	0.25	**3c**	95	100/0
10	*c*-Hex	toluene/Et_2O	20	0.5	**3d**	91	100/0
11	*t*-BuMgBr	toluene/Et_2O	100	2	**3e**[c]	36	100/0
12	PhMgBr	THF	reflux	48			
13		toluene/Et_2O	20	1	**3g**	80	100/0
14	allylMgBr	THF	20	5	**3h**	70	75/25
15		Et_2O	20	1		75	80/20
16		toluene/Et_2O	20	0.1		88	77/23
17		toluene/Et_2O	−50	1		83	82/18
18		CH_2Cl_2/Et_2O	−70	0.25		89	82/18
19		CH_2Cl_2/Et_2O + 1 equiv of $TiCl_4$	−70	0.5		70	96/4

[a] Isolated material. [b] Crude yield. [c] The reduction product **3f** is also obtained in ~20% yield.

Scheme I



Scheme II

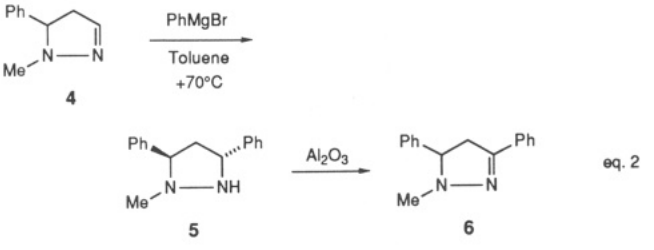


or to a noncoordinating one.[6] Thus, when the same reaction was repeated in toluene, with the minimum amount of Et_2O (coming from the Grignard ethereal solution) the reaction was completed in less than 1 h at room temperature! (see Table I, entry 3). Moreover, the ratio of diastereomers was increased to 6:94. An attempt to attain complete stereocontrol by removal of the Et_2O proved fruitless (entry 4). On the other hand, in a polar noncoordinating solvent, such as CH_2Cl_2, MeMgBr gave the same 6:94 ratio, albeit in a lower yield (70% after 3 h at room temperature). The use of MeMgI (entry 5) or MeMgCl (entry 6), in toluene, gave the same selectivity as MeMgBr, although in the latter case we observed a faster reaction.

The reactivity of other Grignard reagents follows the same trend. BuMgBr does not react in THF, but in toluene the reaction is complete in 30 min and a single diastereomer **3c** is produced (entries 8 and 9). PhMgBr behaves similarly (entries 12 and 13). Even a secondary Grignard reagent, such as cyclohexylmagnesium chloride, react perfectly well (entry 10). tBuMgCl proved less reactive, but upon heating to +100 °C two compounds were obtained, the desired single diastereomer **3e** and the reduction compound **3f** arising either from the decomposition of tBuMgX into isobutene and HMgX or through a 6-membered Meerwein–Pondorf–Verley-like mechanism.

Allyl Grignard reagents are more reactive, and in THF as solvent the reaction proceeded at room temperature, giving the two diastereomers **2h** and **3h** in 25:75 ratio.[7] This ratio was slightly increased by the change of solvent and by the lowering of the reaction temperature (entries 14–18). However, upon precomplexation of **1** with 1 equiv of $TiCl_4$ at −78 °C, and then reaction with allyl Grignard reagent, a 4:96 ratio was attained in favor of **3h**.

This unprecedented increase of reactivity of Grignard reagents toward the hydrazone functionality in toluene solvent was also exploited in the synthesis of C_2 symmetrical 1,3 diamines which were of interest to us. Thus, PhMgBr reacted with pyrazoline **4** at 70 °C in 30 min, in toluene, to afford the pyrazolidine **5** as a single diastereomer (eq 2). Attempted purification of this material



eq. 2

on Al_2O_3 resulted in the oxidation product **6** in 83% isolated yield. The intermediate magnesium hydrazide could be alkylated with dimethyl sulfate[9] to yield the *N,N'*-dimethylated pyrazolidine **7**[10] in 62% isolated yield, again as a single racemic diastereomer, the *d,l* one[11] (eq 3).

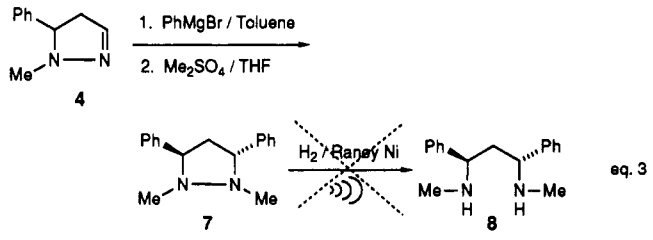
(6) Canonne, P.; Foscolos, G.; Caron, H.; Lemay, G. *Tetrahedron* **1982**, *38*, 3563.

(7) That the major diastereomer was **3h** was proved by cleavage of the N–N bond, under our recently described conditions[6] (with saturation of the allylic double bond), and comparing the ^1H NMR spectra with the same compound obtained with PrLi or PrMgCl (see entry 7).

(8) Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625. In the present case, it is better to use iPrOH as solvent instead of MeOH.

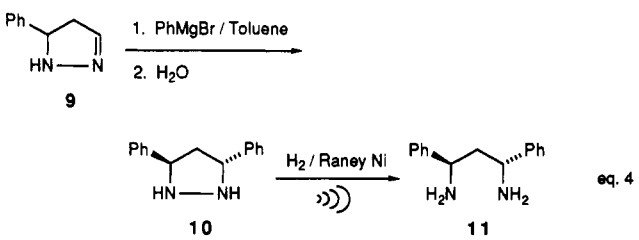
(9) Alkylation with MeI gave a low yield of **7**.

(10) Compound **7** is known to be a powerful fungicide and plant growth inhibitor and is described also in several patents. See among others: (a) Berenson, H. *Chem. Abstr.* **1976**, *84*, 105587j. (b) Cross, B.; Grasso, C. P.; Walworth, B. L. *Chem. Abstr.* **1976**, *85*, 46665d. (c) Shafer, N. E.; Bhalla, P. R. *Chem. Abstr.* **1982**, *96*, 16078z. (d) O'Neal, T. D.; Bhalla, P. R.; Cross, B. *Chem. Abstr.* **1982**, *96*, 47568p. See also a recent preparation: Shimizu, T.; Hayashi, Y.; Miki, M.; Teramura, K. *J. Org. Chem.* **1987**, *52*, 2277.



However, the tetrasubstituted nature of the hydrazine functionality prevented all our attempts to cleave the N–N bond and to obtain the desired diamine 8.

Another approach to the diamine 8 was more successful. Indeed, although less reactive than 4, pyrazoline 9 reacted with PhMgBr in toluene, at 100 °C, for 1 h. Hydrolysis of the reaction mixture gave the unstable pyrazolidine 10 which was cleaved under our recently described conditions[6] (assistance by ultrasound) to yield the pure *d,l* primary diamine 11 in 74% overall yield (eq 4). This diamine was recently obtained and transformed to diamine 8 by Denmark[12] following a similar reaction scheme but using the



pyrazoline 9, protected as the *N*-Boc derivative, and $PhCeCl_2$ instead of PhMgBr.

With these new reaction conditions, we believe that the hydrazone functionality will become a viable alternative to imines which are commonly preferred, due to their higher reactivity.

Supplementary Material Available: Experimental procedures and ^1H and ^{13}C NMR spectra of adducts **3a–h**, pyrazoline **6**, and pyrazolidine **7** (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) The ^1H NMR data of the two diastereomers of 7 are described: Elguero, J.; Marzin, C.; Tizané, J. *Tetrahedron Lett.* **1969**, 513.

(12) Denmark, S. E.; Kim, J.-H. *Synthesis* **1992**, 229.

Regioselective Ring Opening of Cyclopropane by Mercury(II) and Transmetalation of the Intermediate Organomercurial with Lithium and Copper Reagents. A Novel, Stereoselective Approach to Cyclobutanes†

Pavel Kočovský* and Jiří Šrogl

Department of Chemistry, University of Leicester, Leicester LE1 7RH, England

Received May 5, 1992

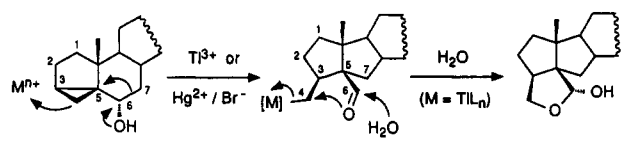
Summary: Cleavage of cyclopropyl derivative 1 by means of Hg^{2+} occurs with a skeletal rearrangement to afford a stable organomercurial 3 which on treatment with Me_2CuLi gives cyclobutanol 9; analogous conjugate addition is also reported (**10** → **15**).

Stereo- and regioselective cleavage of cyclopropanes[1,2] by means of electrophilic metal complexes can serve as an attractive strategy for the construction of up to three contiguous chiral centers.[3]

Recently, we have described a stereospecific, thallium(III)-mediated cleavage of steroidal cyclopropane derivative 1 which triggered a unique skeletal rearrangement affording lactol 4 via the thalliated intermediate 2 (Scheme I).[6] Mercury(II) ion, isoelectronic with Tl(III), is also known to be capable of cleavage of a cyclopropane.[1,5,7] Since organomercurials are generally more stable than their organothallium counterparts, it was of great interest to explore the reactivity of 1 toward Hg(II), aiming at isolation of the organomercurial product and exploration of its reactivity, including transmetalation.

3α,5-Cyclo-5α-cholestan-6α-ol (1)[8] was treated with $Hg(NO_3)_2 \cdot H_2O$ in DME/MeCN (2:5) at rt. The reaction was monitored by TLC, and when the starting material

Scheme I



could no longer be detected (ca. 1.5 h), aqueous KBr was added.[9] The mixture was worked up to afford organo-

† Dedicated to Professor John E. McMurry on the occasion of his 50th birthday.

(1) (a) Rappoport, Z., Ed. *The Chemistry of the Cyclopropyl Group*; J. Wiley and Sons: London, 1987. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245.

(2) Cyclopropanes themselves can be synthesized with high diastereo- and enantioselectivity.[1]

(3) Two mechanisms can be discerned for the ring opening of cyclopropanes, namely the *edge* (favored by reagents capable of back donation, such as transition metals[1] and halogens[4]) and the *corner* cleavage (typical for electrophiles that are incapable of back donation, e.g., H^+, Hg^{2+}, and Tl^{3+}).[5,6]

(4) Lambert, J. B.; Chelius, E. C.; Schulz, W. J., Jr.; Carpenter, M. E. *J. Am. Chem. Soc.* **1990**, *112*, 3156.

(5) (a) Coxon, J. M.; Steel, P. J.; Whittington, B. I.; Battiste, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 2988; *J. Org. Chem.* **1989**, *54*, 1383. (b) Coxon, J. M.; Steel, P. J.; Whittington, B. I. *J. Org. Chem.* **1990**, *55*, 4136. (c) Lambert, J. B.; Chelius, E. C.; Bible, R. H., Jr.; Hajdu, E. *J. Am. Chem. Soc.* **1991**, *113*, 1331.

(6) Kočovský, P.; Pour, M.; Gogoll, A.; Hanuš, V.; Smrčina, M. *J. Am. Chem. Soc.* **1990**, *112*, 6735.

0022-3263/92/1957-4565$03.00/0