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ENANTIOSELECTIVE SYNTHESIS VIA THE NUCLEOPHILIC ALKYLATION OF HYDRAZONES : ACETALS AS CHIRAL AUXILIARIES.

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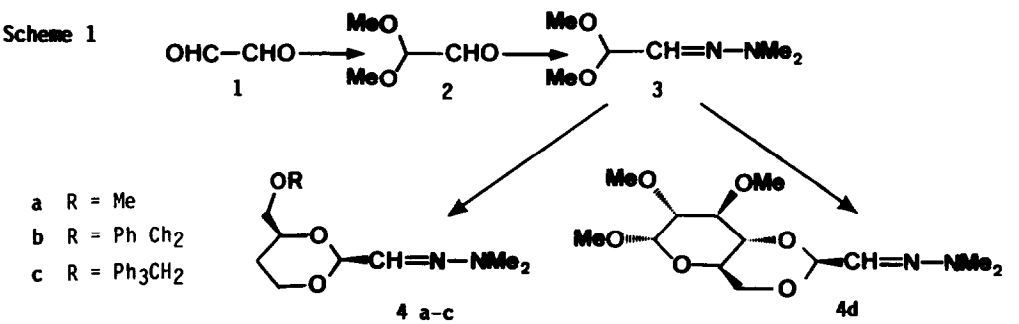
Summary : Diastereoselective addition of organolithium reagents on hydrazones vicinal to chiral cyclic acetals provide chiral hydrazinoacetals from which optically active aminoacetals and aminoacids can be prepared.

Recently the syntheses of optically active amines involving the addition of organometallic reagents on chiral hydrazones of aldehydes as the key step have appeared in the literature (1-5). Good diastereo and enantioselectivities were observed when hydrazones obtained from chiral N-aminoephedrine or proline-derived hydrazines were reacted respectively with either Grignard (1) or organolithium (2) and organocerium (3,4) reagents. In the third case, the oxygenated substituent of the proline-derived part of the hydrazone was systematically changed in order to optimize the selectivity (4). The coordination of the metal by the nitrogen atoms of the hydrazone and the oxygen atom(s) of the substituent initially present in the amine is thought to account for the facial diastereoselection. Few attempts have been made to impart a coordination role to the moiety of the hydrazone deriving from the aldehyde itself. Claremon et al (5) have shown that α-alkoxyhydrazones react with organolithium compounds to afford the threo 2-aminoalcohols derivatives with a good diastereoselectivity. The authors initiated their synthesis from optically active aromatic alcohols and, eventually using kinetic resolution, they obtained the optically active norpseudoephedrines.

We report herein our first results on the use of cyclic acetals as chiral auxiliaries, for the diastereofacial differentiation during the addition of organometallics on a vicinal hydrazone function. The hydrazone-acetals (6) were obtained from glyoxal, previously studied in our laboratory from the point of view of its dissymmetrisation (7).

Scheme 1



We have found that the acetalization of monohydrazones (8) of glyoxal is rather uneasy, due to their stability, whereas the preparation of hydrazones from the monoacetals of glyoxal is a straightforward process. Therefore, the first step of our strategy was the monoacetalization of glyoxal. We have previously described (7) this reaction with alkanols. Attempts to obtain correct yields in the monoacetalization of glyoxal by diols were unsuccessful, and therefore we used a transacetalization step (scheme 1, **3** → **4**). Contrary to the aldehydes or imines, the hydrazones remain unchanged during this step regardless of the diol used.

In an effort to optimize the diastereoselectivity of the nucleophilic addition of organometallics on the C = N bond (scheme 2, **4** → **5**), we tested the acetals issued from diols prepared from malic acid **4a** - **4c** in which the R group of the alkoxymethyl substituent was varied from methyl to trityl, as well as some sugar-derived acetals such as **4d**.

The results of the addition (9, 10) of MeLi and nBuLi (ether, -12°C, 3h, R^1Li 3 eq) are reported in table I.

Table I : **Addition of R^1Li to acetals hydrazones 4 a - d (11)**[1]

4 / R^1Li	4 a		4 b		4 c		4 d	
	Y %	d	Y %	d	Y %	d	Y %[2]	d
MeLi	78	80/20	72	90/10	72	100/0	80	95/5
nBuLi	75	70/30	74	80/20	76	92/8	72	96/4

[1] d = diastereoselectivity. [2] R^1Li 5 equivalents.

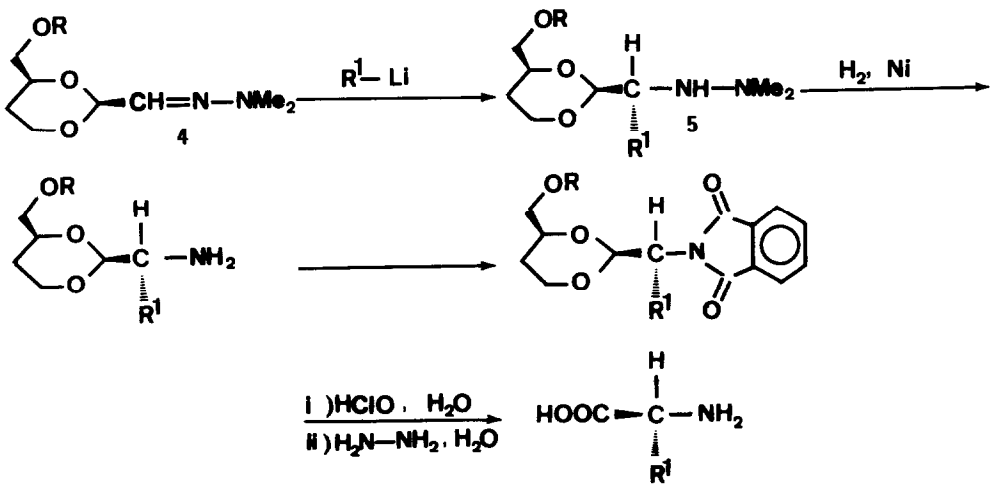
The best diastereoselectivity obtained was with the sterically demanding substituted acetal **4c**, followed by the glucose-derived acetal **4d**. When we compared nBuLi to MeLi, we noticed a lower diastereoselectivity in all cases except with the acetal **4d**. ^{13}C nmr chemical shifts indicated that, in the series **4a** - **4c**, the major isomers had the same stereochemical structure, and thus the role of the substituent is clearly due to steric hindrance.

As with the α-alkoxyhydrazones (5), the observed diastereoselectivity presumes a chelation controlled 6-membered intermediate, in which only one of the two acetalic oxygen atoms is involved. In accordance with our results, the oxygen atom selected to form the chelate is the farthest from the voluminous substituent.

According to this pattern, as shown by the inspection of molecular models, the nucleophilic attack takes place on the re face of the C = N bond in the case of acetal **4c** issued from S(-)-malic acid.

These conclusions were corroborated by the sequential reactions providing optically active α-aminoacids. Thus, the reductive cleavage of the hydrazine **5c** (R^1 = Me) (H_2, Raney nickel, EtOH, trace of KOH, 20 bars, 40°C, 4h), followed by oxidation of the phtalimido derivative of the amine (i : HClO, pH = 4, acetone, 0 - 5°C, 3h ; ii : H_2N-NH_2, H_2O, rt, 15h) provided L(+)-alanine from S(-)-malic acid as expected. No racemization was detected by nmr in the intermediate steps. The aminoacid was obtained with 97 % optical purity.

Scheme 2 :



The method described here provides a facile route for the preparation of optically active α-aminoacids starting from glyoxal using simple reactions. It is possible to obtain both configurations, starting from R and S malic acids. The optically active α-hydrazinoacetals **5** are obviously not only precursors of aminoacids, as shown here, but also of aminoalcohols and other amino derivatives with masked aldehyde function. We are currently working on broadening the scope of the nucleophilic addition on hydrazones **4** and the uses of hydrazinoacetals **5** in synthesis.

References and notes

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6 - Neither hydrazono nor hydrazino chiral α-acetals had been reported to our knowledge.

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9 - Only moderate diastereoselectivities were observed in the case of acetals formed with 1,4-dialkoxy 2,3-diols issued from tartaric acid.

10 - The syntheses of chiral diols and acetals will be reported elsewhere.

11 - Spectroscopic data:

- Hydrazinoacetals **5** (major isomers).

5a, R^1 = Me. ^1H nmr : 4.2 (d, J = 6Hz, 1H) ; 4 - 3.5 (m, 5H) ; 3.3 (s, 3H) ; 2.8 (m 1H) ; 2.3 (s, 1H, NH) ; 2.2 (s, 6H ; 1.9 - 1.3 (m, 2H) ; 1 (d, J = 9Hz, 3H). ^{13}C nmr 102.0 (CH) ; 76.0 (CH_2) ; 75.0 (CH_2) ; 60.0 (CH) ; 56.0 (CH_3) ; 48.0 (CH_3) ; 28.0 (CH_2) 15.0 (CH_3).

5a, R^1 = nBu. ^{13}C nmr 101.3 (CH); 75.6 (CH) ; 75.5 (CH_2) ; 66.3 (CH_2) ; 60.5 (CH_3) 59.2 (CH) ; 47.9 (CH_3) ; 28.3 (CH_2); 28.0 (CH_2) ; 27.64 (CH_2) ; 23.0 (CH_2) ; 14.0 (CH_3).

5b, R^1 = Me. ^1H nmr 7.5 (m, 5H) ; 4.5 (s, 2H) ; 4.3 (d, J = 6Hz, 1H) ; 4 - 3.6 (m, 1H) 2.3 (s, 6H) ; 1.9 - 1.3 (m, 2H) ; 1.1 (d, J = 8Hz, 3H). ^{13}C nmr : 138.2 (C) ; 128.3 (CH) 127.6 (CH) ; 102.2 (CH) ; 75.9 (CH); 73.4 (CH_{2X}) ; 72.8 (CH_2) ; 66.3 (CH_2) ; 55.8 (CH) 48.1 (CH_3) ; 28.1 (CH_2) ; 14.9 (CH_3).

5b, R^1 = nBu. ^{13}C nmr : 130.0 (C) ; 128.0, 127.0 and 126.0 (CH aromatique) ; 101.0 (CH) 80.0 (CH_2) ; 76.0 (CH) ; 72.0 (CH_2) ; 56.0 (CH) ; 48.0 (CH_3) ; 29.0 (CH_2) ; 28.2 (CH_2) 27.0 (CH_2) ; 22.0 (CH_2) ; 13.0 (CH_3).

5c, R^1 = Me. ^1H nmr : 7.7 - 7.1 (m, 15H) ; 4.3 (d, J = 8Hz, 1H) ; 4.1 - 3.8 (m, 1H) 3.7 - 3.4 (t, 2H) ; 3.1 (d, J = 6Hz, 2H) ; 3 - 2.6 (m, 1H) ; 2.4 (s, 1H) ; 2.3 (s, H) 1.9 - 1.4 (m, 2H) ; 1.0 (d, J = 5Hz, 3H). ^{13}C nmr : 144.0 (C) ; 128.7 (CH) ; 127.7 (CH) 126.9 (CH) ; 102.4 (CH) ; 86.3 (C) ; 75.9 (CH) ; 66.5 (CH_2) ; 66.3 (CH_2) ; 55.9 (CH) 48.3 (CH_3) ; 28.4 (CH_2) ; 14.8 (CH_3).

5c, R^1 = nBu. ^1H nmr : 7.7 - 7.1 (m, 15H) ; 4.4 (d, J = 8Hz, 1H) ; 4.1 - 3.8 (m, 1H) 3.7 - 3.4 (t, 2H) ; 3.2 (d, J = 6Hz, 2H) ; 3 - 2.6 (m, 1H) ; 2.5 (s, 1H) ; 2.4 (s, 1H) 1.9 - 1.0 (m, 11H). ^{13}C nmr : 144.1 (C) ; 128.8 (CH) ; 127.8 (CH) ; 127.0 (CH) ; 101. (CH) ; 86.3 (C) ; 76.1 (CH) ; 66.6 (CH_2) ; 66.5 (CH_2) ; 60.6 (CH) ; 48.2 (CH_3) ; 28. (CH_2) ; 28.3 (CH_2) ; 28.1 (CH_2) ; 23.3 (CH_2) ; 14.2 (CH_3).

5d, R^1 = Me. ^{13}C nmr : 103.1 (CH) ; 98.5 (CH) ; 82.1 (CH) ; 81.2 (CH) ; 79.9 (CH) ; 68. (CH_2) ; 62.0 (CH) ; 60.5 (CH_3) ; 59.3 (CH_3) ; 55.4 (CH_3) ; 55.0 (CH) ; 48.1 (CH_3) ; 15. (CH_3).

5d, R^1 = nBu. ^{13}C nmr : 102.1 (CH) ; 98.4 (CH) ; 82.0 (CH) ; 81.7 (CH) ; 79.9 (CH) 68.6 (CH) ; 60.6 (CH) ; 59.8 (CH_3) ; 59.3 (CH_3) ; 55.0 (CH_3) ; 68.0 (CH_3) ; 28.8 (CH_2) 27.8 (CH_2) ; 23.0 (CH_2) ; 14.0 (CH_3).

- Aminoacetal **6c**, R^1 = Me. ^1H nmr : 4.5 (d, J = 6Hz, 1H) ; 4.1 - 3.5 (m, 5H) ; 3.3 (s 3H) ; 2.9 (s, 2H) ; 2.5 (m, 1H) ; 1.2 (d, J = 8Hz, 1H). ^{13}C nmr : 104.0 (CH) ; 75.5 (CH_2) 66.0 (CH_2) ; 59.0 (CH_3) ; 49.0 (CH) ; 28.0 (Ch_2) ; 18.0 (CH_3).

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