THE REACTION OF TETRAZOLYLIMINES WITH GRIGNARD REAGENTS

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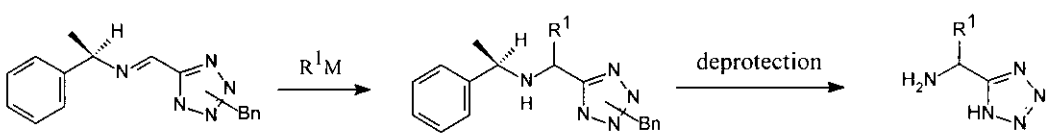
Abstract *- The addition of alkyl Grignard reagents on 1-benzyltetrazole imines occurs at the nitrogen atom to give the corresponding N-alkylated tetrazole amines (the azophilic product). In contrast the same reagents on the 2-benzyltetrazole imines exclusively attack the imino carbon (the carbophilic product).*

Numerous tetrazole derivatives possese various biological activity and this is mainly due to the fact that, in many cases, a tetrazole functional group serves successfully as a metabolically stable isostere for a corresponding carboxylic acid.[1] Recently, particularly in connection with the development of nonpeptidic receptor antagonists of the vasoactive octapeptide angiotensin II, there has been renewed interest in the chemistry of tetrazoles.[2] In connection with our research programs of designing enzyme inhibitors and receptor antagonists, we needed various tetrazole analogs as amino acid isosteres.[3] To this end, we have examined a synthetic methodology based on a nucleophilic addition of the Grignard reagents on imines and herein we would like to report unexpected findings regarding the regioselectivity in the addition reaction.

There are numerous literature precedents on this type of reactions and it has been known that in most cases the organometallic addition to imines proceeds with a nucleophile attack normally on the carbon atom (carbophilic addition) instead of the nitrogen atom (azophilic addition).[4] This type of the reaction, particularly, the reaction of organometallic reagents with chiral imines has been successfully used for the preparation of various nitrogen containing natural products and bioactive compounds.

Scheme 1

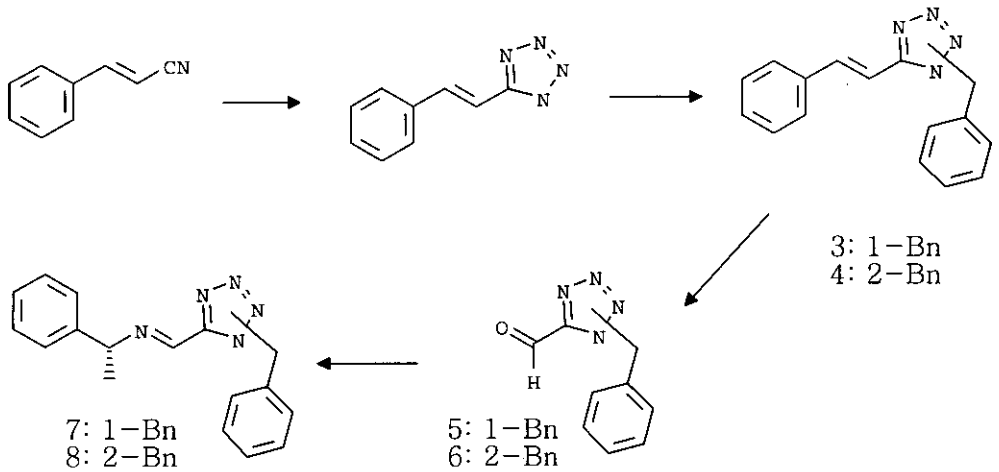


7 or 8 **9 or 10** **11**

Accordingly our synthetic strategy for the preparation of the aminomethyltetrazole derivatives was planned as depicted in Scheme 1. The key intermediates **(7,8)** were prepared from cinnamonitrile as shown in Scheme 2. Vinyltetrazole **(2)**, obtained from cinnamonitrile and sodium azide, was protected with a benzyl group.

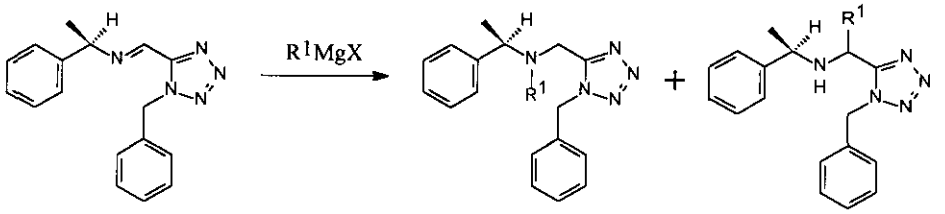
Two benzylated isomers, purified chromatographically, were ozonolyzed to give the corresponding aldehydes **(5,6)** which reacted immediately with optically pure phenethylamine to give tetrazole imines **(7,8)**.[5]

Scheme 2



First we examined the addition reaction on imine **(7)** with various Grignard reagents. The addition of methylmagnesium bromide on **(7)** proceeded smoothly to give exclusively the addition product **(9b)** on the carbon atom (the carbophilic addition). In contrast the reaction with ethylmagnesium bromide produced **(9a)** exclusively in which the addition occurs on the nitrogen atom (the azophilic addition). The same azophilic product was also obtained with isopropyl- and benzylmagnesium chlorides. This result indicates that the reacting site is determined by the type of the Grignard reagent being used. This azophilic addition is quite unusual although there are few examples known for nucleophile attacks on certain electrophilic nitrogen derivatives such as oximes[6] or oxime tosylates.[7] Another known cases for the azophilic addition are when the imine carbon atom is much more hindered than the imine nitrogen atom or when imines were substituted with strong electron withdrawing groups as in the case of fluorenimines and *N*-alkyltetraphenylcyclopentadienimines.[8] It was also known that the reaction of the a-imino ester with simple Grignard reagents such as ethyl-, *i*-propyl- and benzylmagnesium halides gave the azophilic products.[9,10]

Table 1. Nucleophilic addition of Grignard reagent to 1-Benzyltetrazole imine



7 **9a** **9b**

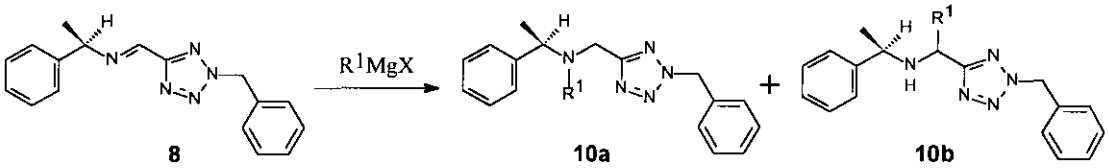
Entry	R^1MgX	9a : 9b	Yield[a] (%)
1	MeMgBr	0 : 100	51[b]
2	EtMgBr	100 : 0	85
3	*i*-PrMgCl	100 : 0	81
4	BnMgCl	100 : 0	76
5		45 : 55	72

[a] Yields after purification by chromatography on silica gel preparative TLC

[b] The ratio of two diastereomers is 2:1

However, when we examined the same addition reaction with 2-benzyltetrazole imine **(8)**, we obtained the products in which the Grignard reagents attack predominantly the imino carbon *via* carbophilic addition. Especially with benzyl and allyl Grignard reagents we obtained almost exclusively the carbophilic products (Table 2).

Table 2. Nucleophilic addition of Grignard reagent to 2-Benzyltetrazole imine



8 **10a** **10b**

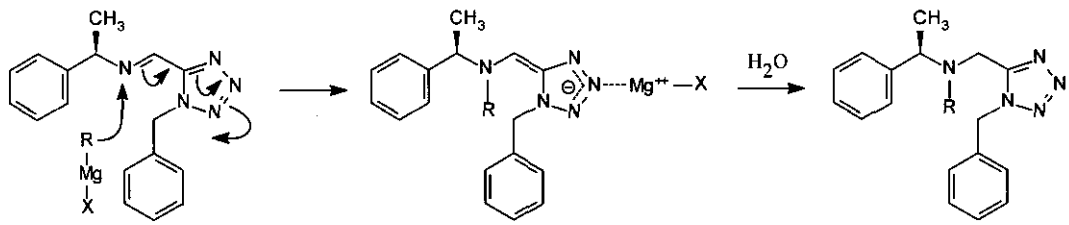
Entry	R^1MgX	10a : 10b	Yield (%)
1	MeMgBr	0 : 100	58
2	EtMgBr	24 : 76[a]	54
3	*i*-PrMgCl	64 : 36	41
4	BnMgCl	5 : 95	75
5		1 : 99	61

[a] The ratio of two diastereomers is 3:7

The reason for the azophilic addition is probably due to the anion stabilizing ability of the tetrazole group (Scheme 3). In this aspect the 1-benzyl isomer is expected to have more stabilizing effect than the 2-benzyl isomer because of an additional conjugation. One indirect evidence for this electron withdrawing effect can be found from the ^{1}H and ^{13}C chemical shifts of the phenethyl group. Thus, in 1-benzyl isomer the methine proton adjacent to the imino nitrogen is 0.6 ppm and the carbon is 18 ppm downfield than the 2-benzyl isomer, respectively. This suggests that the imino nitrogen is more positively polarized in the 1-benzyl isomer than the 2-benzyl isomer which would favour the azophilic addition in the 1-benzyl isomer.

We also examined the addition reaction of imines **(7)** and **(8)** with other organometallic nucleophiles such as alkyllithiums and cuprates. However, we failed to obtain neither of carbophilic or azophilic products indicating that this unusual azophilic addition seems to be unique for the Grignard reagent. It is not clear at this moment why this unusual reaction is unique for the Grignard reagent type nucleophiles. A scope of this reaction and a possible mechanism for the reaction are subjects for our current study.

Scheme 3



A typical reaction condition is as follows; To a solution of imine **(7)** (0.10 g, 0.34 mmol) in dry diethyl ether (8 mL) was added ethylmagnesium bromide (0.25 mL of 3M solution, 0.75 mmol) at 0°C. After 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and then extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated to give the crude product which was purified by prep TLC (silica gel, hexane/ethyl acetate (3/1)) to give the azophilic addition product **(9a)** (91.7 mg, 85%).[11] We could also obtain the carbophilic addition product **(10b)** from **(8)** under the same conditions.[12]

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5. ***N*-(R)-a-Methylbenzyl-1-benzyl-5-tetrazole imine(7)**: ^{1}H-NMR (300 MHz,$CDCl_3$), δ7.67 (1H, d, J=7.2 Hz), 7.45-7.26 (10H, m), 5.94 (2H, dd, J=14.0 and 14.0 Hz), 5.24 (1H, quintet, J=7.2 Hz), 1.59 (2H, d, J=7.2 Hz); ^{13}C-NMR (75 MHz,$CDCl_3$), δ154.08, 146.44, 141.68, 133.83, 128.92, 128.79, 127.90, 126.09, 52.58, 49.61, 21.74, 17.77; IR (KBr):1659, 1563, 716 cm^{-1}; MS $^m/_z$ 292(M^+). ***N*-(R)-a-Methylbenzyl-2-benzyl-5-tetrazole imine(8)**: ^{1}H-NMR (300 MHz, $CDCl_3$), δ8.50 (1H, s), 7.42-7.20 (10H, m), 5.78(2H, s), 4.65 (1H, q, J=6.6 Hz), 1.65 (3H, d, J=6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$), δ162.83, 148.25, 143.26, 132.78, 129.10, 129.02, 128.57, 128.50, 127.30, 126.87, 70.52, 57.08, 23.98; MS $^m/_z$ 292(M^+).

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11. **Spectroscopic data for 9a (R^1=Et)** : ^{1}H-NMR (300 MHz, $CDCl_3$), δ7.32-7.23 (8H, m), 6.96-6.92 (2H, m), 5.45 (2H, dd,J=15.2 and 15.2 Hz), 3.88 (1H, q, J=6.8 Hz), 3.78 (2H, dd, J=14.2 and 14.2 Hz), 2.65 (1H, hex, J=6.6 Hz), 2.39 (1H, hex, J=6.6 Hz), 1.35 (3H, d, J=6.7 Hz), 0.96 (3H, t, J=6.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$), δ152.98, 142.23, 133.66, 128.85, 128.43, 127.79, 127.41, 127.39, 58.53, 50.39, 43.95, 42.51, 15.14, 11.69); IR (KBr):1459, 731 cm^{-1}.

12. **Spectroscopic data for 10b (R^1=Et, diastereomeric mixture)**: ^{1}H-NMR (300 MHz, $CDCl_3$), δ7.38-7.15 (10H, m), 5.81-5.66 (2H, m), 3.98 (0.3x1H, t, J=6.8 Hz), 3.65 (0.7x1H, t, J=7.0 Hz), 3.45 (0.7x1H, q, J=6.5 Hz), 3.15 (0.3x1H, q, J=6.5 Hz), 1.80 (1H, br s), 1.85-1.72 (2H, m), 1.33 (0.3x3H, d, J=6.5 Hz), 1.24 (0.7x3H, d, J=6.5 Hz), 0.84-0.75 (3H, m); ^{13}C-NMR (75 MHz, $CDCl_3$), δ169.45, 169.15; 145.27, 144.97; 133.48, 133.38; 129.32, 129.12; 128.94, 128.84; 128.82, 128.62; 128.34, 128.25; 128.23, 128.17; 126.93, 126.87; 56.57, 56.52; 55.59, 55.55; 53.46, 53.22; 29.12, 27.97; 25.06, 23.12; 10.40, 9.99.

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