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Stereoselective Grignard additions to N-formyl hydrazone: a concise synthesis of Noxafil^R side chain and a synthesis of Noxafil^R

Anil K. Saksena,[a,*] Viyyoor M. Girijavallabhan,[b] Haiyan Wang,[b] Raymond G. Lovey,[b] Frank Guenter,[c] Ingrid Mergelsberg[c] and Mohinder S. Puar[b]

[a]*53, Beverley Road, Upper Montclair, NJ 07043, USA*
[b]*Schering-Plough Research Institute, 2015, Galloping Hill Road, Kenilworth, NJ 07033, USA*
[c]*Werthenstein Chemie AG, CH-6105 Schachen, Switzerland*

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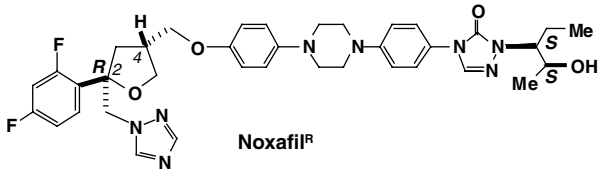
Abstract—Addition of ethyl Grignard reagent to the formyl hydrazone **11** via in situ silylation provided the corresponding formyl hydrazine with excellent diastereoselectivity in favor of the desired *S*,*S*-diastereoisomer **6**. Treatment of **6** with the phenyl carbamate **13** efficiently provided the O-benzyl protected Noxafil, which was deprotected to provide Noxafil^R.

Noxafil^R is a novel 2,2,4-trisubstituted tetrahydrofuran based antifungal agent, which has successfully undergone phase III clinical trials. It has shown improved therapeutic potential over existing drugs against a variety of invasive fungal infections in normal and immunocompromised patients refractory to or intolerant of standard therapy.[1]



A major improvement in the synthesis of Noxafil^R would be an efficient synthesis of the *S*,*S*-hydroxy side chain in the form of the N-formyl hydrazine intermediate **6**. The existing route to this key intermediate is a protracted low yielding sequence as shown in Scheme 1.[2]

The main inefficiency in the above sequence lay in the necessity to obtain the pure *S*,*S*-enantiomer **5** via crystallization from the dibenzoyl-D-tartaric acid salt. A more direct route to the formyl hydrazine **6** was desired. We now describe below the successful outcome of these experiments.

Stereoselective addition of EtMgBr to the aldhydrazone **11** would constitute the most direct route to **6**. Examples of such Grignard additions to C=N are not too common[3,4] and no examples could be found for additions to formyl hydrazones. Jager and co-workers have described additions of Grignard reagents to lactaldehyde derived benzyl imine **7** in a stereoselective manner to favor the *S*,*S*-diastereoisomer **8**[5] (Scheme 2).

The chiral (*S*)-N,N-tetramethyleneacetamide **1** was prepared from ethyl (*S*)-lactate according to Terashima and co-workers.[6,7] Treatment of **1** with Red-Al provided the (*S*)-2-benzyloxy propanal **10** in 94% yield.[8] Formyl hydrazine reacted quite readily with **10** providing the formyl hydrazone **11** as a low melting crystalline solid in >80% yield.[9] Reaction of **11** with EtMgBr (4 equiv; 0 °C to rt) gave a mixture of the desired *S*,*S*-diastereoisomer **6** and its *S*,*R*-diastereoisomer **12** with excellent diastereoselectivity (**6**:**12**, 94:6) in 55% yield (Scheme 3).

In order to improve yields and diastereoselectivity, the hydrazone **11** was silylated in situ before addition of the Grignard reagent. Silylation was also expected to block deprotonation site thereby reducing the amount of Grignard reagent. A dramatic improvement in diastereoselectivity was observed. The yields were slightly

* Corresponding author. E-mail: anilsaksena@cs.com

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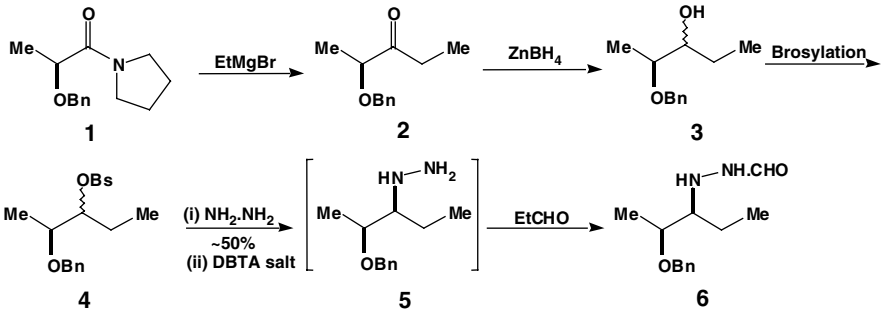
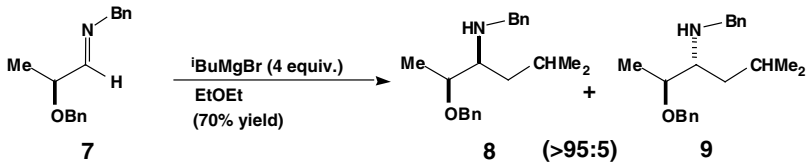
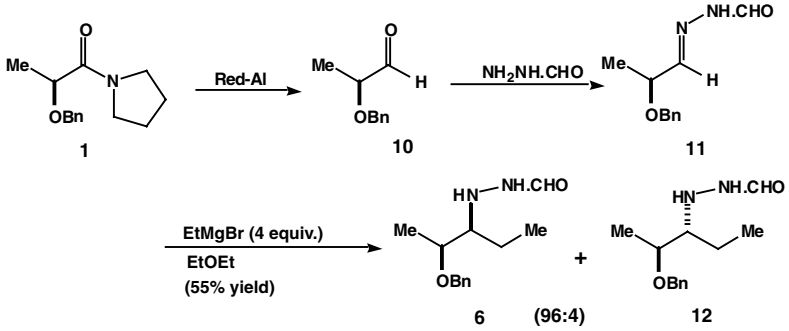


Scheme 1.



Scheme 2.



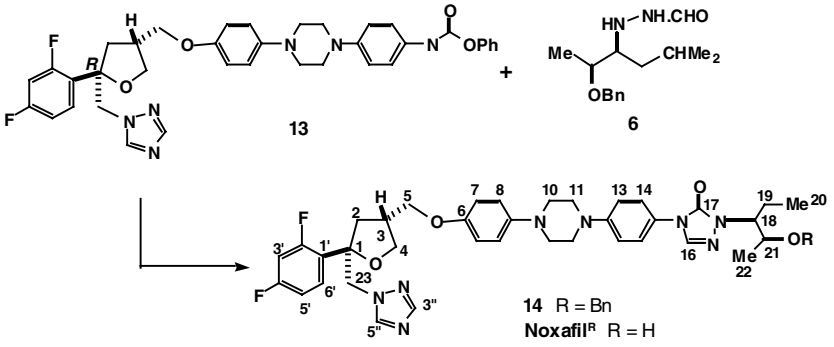
Scheme 3.

improved but the minimum EtMgBr required remained the same. Ethyl magnesium bromide was also found to be better than ethyl magnesium chloride in terms of diastereoselectivity (Table 1).

The formyl hydrazine **6** obtained according to (b)[10,11] was subjected to treatment with the phenyl carbamate **13** to provide the O-benzyl protected Noxafil **14** in

Table 1.

Conditions	**6**:**12**	Yield (%)
(a) 11 + BSA (1.2 equiv) + EtMgBr (4 equiv)	99.4:0.6	57
(b) 11 + BSA (2.0 equiv) + EtMgBr (4 equiv)	99.8:0.2	62.3
(c) 11 + BSA (0 equiv) + EtMgCl (4 equiv)	95:5	53
(d) 11 + BSA (2.0 equiv) + EtMgCl (4 equiv)	98:2	59



Scheme 4.

85% yield. Its deprotection with Pd/C and HCOOH furnished pure Noxafil[R] mp 164–165 °C, $[\alpha]_D^{25} - 29$ (*c* 1.00, $CHCl_3$)[12,13] (Scheme 4).

Acknowledgements

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References and notes

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7. Yields refer to isolated products and have not been optimized. All new compounds were characterized by PMR, CMR, and high resolution mass spectra. When necessary diff NOE, COSY, and NOESY spectra were obtained. Elemental analysis were obtained for crystalline compounds only. Selected spectral data is given here.
8. Preparation of (*S*)-2-benzyloxy propanal **10**: Benzyloxy amide **1** (10 g, 42.8 mmol) was dissolved in toluene (40 mL) and the stirred solution cooled in ice–MeOH bath. To this solution was slowly added Red-Al (3.4 M in toluene; 8.5 mL, 29 mmol). After stirring for 5 h the solution was quenched with acetone (5 mL) and 2 N HCl (70 mL) was added. The product was extracted with EtOAc and the EtOAc phase was washed with water and saturated NaCl. After drying over Na_2SO_4, the solvent was evaporated in vacuo to obtain **10** as a thick oil (6.6 g; 94% yield).
9. Preparation of formyl hydrazone **11**: N-Formyl hydrazine (2.63 g; 43.4 mmol) was dissolved in methanol and mixed with (*S*)-2-benzyloxy propanal **10** (6 g; 36.5 mmol). The resulting solution was stirred overnight. Methanol was evaporated in vacuo and the residue was redissolved in Et_2O. The precipitate was removed by filtration and the filtrate evaporated in vacuo to provide a residue, which was purified on a silica gel column (20% EtOAc/*n*-hexane) to obtain the formyl hydrazone **11** as a waxy solid (6.02 g; 80% yield).
10. Preparation of formyl hydrazine **6**: Formyl hydrazone **11** (4 g; 19.4 mmol) was dissolved in anhydrous diethyl ether (400 mL) and treated with bis(trimethylsilyl) acetamide (BSA) (7.89 g; 38.8 mmol). The solution was stirred at room temperature for 45 min and then cooled (ice-bath) for 15 min. EtMgBr (3 M in Et_2O; 25.86 mL; 77.6 mmol) was added and the solution stirred overnight at room temperature. The reaction was quenched with water and the product was extracted with Et_2O. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to dryness in vacuo to provide a residue, which was purified on a silica gel column (20% EtOAc/*n*-hexane) to provide formyl hydrazine **6** (2.52 g; 62.3% yield) as a colorless oil.
11. The diastereoisomeric ratio was determined by treating a small aliquot of the product with phenyl isocyanate to provide a phenyl urea derivative and determining HPLC on a reverse phase C18 (100 A, 3.9 × 300 mm) column using MeOH–H_2O (66:34) containing 0.1% TFA, against authentic **6** and **12** provided by Dr. D. R. Andrews et al.[2] Retention time **6** 9.3 min; retention time **12** 8.0 min.
12. (−)-4-[4-[4-[4-[[(2*R*-*cis*)-5-(2,4-Difluorophenyl)-tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)furan-3-yl]methoxy]phenyl]-2,4-dihydro-2-[(*S*)-1-ethyl-2(*S*)-hydroxypropyl]-3H-1,2,4-triazol-3-one, (Noxafil[R]): A solution of the phenyl carbamate **13** (4 g; 6 mmol) in toluene (150 mL) was treated with the formyl hydrazine (1.56 g; 6.6 mmol) and DBU (0.1 g; 0.66 mmol). The mixture was stirred at 80 °C (bath temp) and then overnight at 100–110 °C (bath temp). Toluene was evaporated off in vacuo and the residue was purified by chromatography on silica gel (80% EtOAc/*n*-hexane) to provide **14** as a foamy solid (4.03 g; 85% yield). It was dissolved in formic acid (70 mL) and treated with 5%Pd/C (8 g) at 20 °C. The resulting mixture was stirred at 20 °C for 15 h, then heated to 35–40 °C and stirred for an additional 24 h. The mixture was cooled to 20 °C and filtered through Celite washing the filter cake with ~40 mL formic acid and then with two 35 mL portions of MeOH. The filtrate and washings were combined and concentrated in vacuo at 65 °C to a residue, which was chromatographed on silica gel (5% MeOH/CH_2Cl_2) to provide Noxafil[R] (3/44 g; 84% yield) as a crystalline solid (from acetonitrile), mp 164–165 °C.
13. Noxafil[R]: ^{1}H NMR (DMSO-d_6, δ, ppm) 2.15 (dd, J = 13, 8 Hz, 2H$_a$), 2.40 (multiplet, J = 13, 8, 2 Hz, 2H$_b$), 2.55 (multiplet, 3H), 3.75 (multiplet, 4H$_a$), 6.80 (dd, J = 9, 2 Hz, 2H, 7,7′H), 6.94 (dd, J = 9, 2 Hz, 2H, 8,8′H), 3.15 (multiplet, 4H, 10,10′H), 3.32 (multiplet, 4H, 11,11′H), 7.10 (dd, J = 9, 2 Hz, 2H, 13,13′H), 7.50 (dd, J = 9, 2 Hz, 2H, 14, 14′H), 8.34 (s, 16H), 3.79 (multiplet, 18H), 1.70 (multiplet, 2H, 19H), 0.74 (triplet, J = 7 Hz, 3H, 20H), 4.18 (multiplet, 21H), 4.65 (d, J = 5 Hz, 21-OH), 1.12 (doublet, J = 7 Hz, 3H, 22H), 4.57 (d, J = 15 Hz, 23H$_a$), 4.62 (d, J = 15 Hz, 23H$_b$), 6.95 (multiplet, J = 8, 8, 2 Hz, 3′H), 7.28 (multiplet, 2H, 5′,6′H), 7.78 (s, 3″H), 8.32 (s, 5″H).
^{13}C NMR (DMSO-d_6, δ, ppm) 83.2 ($^3J_{CF}$=4 Hz, C-1), 37.5 ($^4J_{CF}$ = 3 Hz, C-2), 38.3 (C-3), 69.8 (C-4), 68.6 (C-5), 152.1 (C-6), 114.9 (C-7, -7′), 117.5 (C-8, -8′), 125.4 (C-9), 49.5* (C-10, -10′), 48.2* (C-11, -11′), 149.7 (C-12), 115.6 (C-13, 13′), 122.7 (C-14, -14′), 145.3 (C-15), 135.0 (C-16), 152.0 (C-17), 57.7 (C-18), 26.1 (C-19), 10.5 (C-20), 70.7 (C-21), 16.4 (C-22), 55.1 ($^4J_{CF}$ = 3 Hz, C-23), 126.1 ($^2J_{CF}$ = 13 Hz, $^4J_{CF}$ = 4 Hz, C-1′), 161.8 (J_{CF} = 246 Hz, $^3J_{CF}$ = 12 Hz, C-2′), 104.4 ($^2J_{CF}$ = 26, 27 Hz, C-3′), 158.6 (J_{CF} = 247 Hz, $^3J_{FC}$ = 13 Hz, C-4′), 110.9 ($^2J_{CF}$ = 21 Hz, $^4J_{CF}$ = 3 Hz, C-5′), 128.4 ($^3J_{CF}$ = 10, 6 Hz, C-6′), 150.4 (C-3″), 144.9 (C-5″). *Assignments interchangeable.
MS (EI) 700 (M+), 698 (M−2), 685 (M−15), 655 (M−45), 618 (M−82), 600 (M−100), 425, 423, 422, 399, 328, 302, 301, 278, 262, 229, 195, 141, 127.
Elemental analysis: found: C, 63.38; H, 5.95; N, 16.03; F, 5.68; calcd for $C_{37}H_{42}F_2N_8O_4$: C, 63.43; H, 6.00; N, 16.00; F, 5.43.