Total Regio- and Stereoselective Synthesis of Perhydropyrrolo[3,4-c]pyrazole Derivatives by [3+2] Intramolecular Dipolar Cycloaddition Reaction on Chiral Perhydro-1,3-benzoxazines

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Abstract: Reaction of N-acyl- N'-methyl- or N-acyl- N'-phenylhydrazines with chiral 3-allyl-2-formylperhydro-1,3-benzoxazines form azomethine imines that cyclize to give perhydropyrrolo[3,4-c]pyrazole derivatives. The dipolar cycloaddition was totally regio- and stereoselective yielding a single diastereoisomer. The reaction conditions and the yields of the final compounds are dependent on the substitution pattern of the olefinic bond.

Key words: asymmetric synthesis, azomethine imines, dipolar cycloaddition, pyrazolidines, stereoselective synthesis

[3+2] Dipolar cycloaddition of 1,3-dipoles containing nitrogen atoms to unsaturated substrates constitutes one of the simplest ways to the regio- and stereoselective construction of five-membered nitrogen heterocycles.1 In this respect, nitrones,2 nitrile oxides5 and azomethine ylides4 have been widely used, whereas other nitrogen-containing 1,3-dipoles such as azomethine imines,5 although well known since the 60’s,6 have been employed much less.

Due to the interest of azomethine imines as 1,3-dipoles, there are several synthetic methods directed to the generation of this kind of intermediates. In this respect, azomethine imines have been prepared from protonated hydrazones7 or hydrazones by tautomerization via a thermal 1,2-hydrogen shift.8 α-Silylnitrosamines were also easily transformed into azomethine imines by thermally promoted 1,4-silatropic shift of the silyl group to the oxygen atom of the nitroso group.9 Some other reactions such as catalytic dehydrogenation of trisubstituted hydrazines,10 thermal carbon–nitrogen bond cleavage of aziridines bearing electron-withdrawing groups,11 or thermal or photochemical decomposition of sydrones12 have been also successfully used in the generation of azomethine imines. Nevertheless, the most general and common way to these intermediates is the condensation of N-acyl- N'-alkylhydrazines with aldehydes and ketones.13

The intramolecular version of this reaction results in the formation of new fused or bridged diazabicyclic system and takes place easily with unactivated dipolarophiles such as terminal alkenes, and often turns out with excellent diastereofacial discrimination exhibiting high stereoselectivity.14 However, the use of azomethine imines in asymmetric 1,3-dipolar cycloaddition reactions is very limited.15

We have recently reported the utility of chiral perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol in the synthesis of enantiopure octahydropyrrrolo[3,4-b]pyrroles by intramolecular 1,3-dipolar cycloaddition of azomethine ylides.16 In this paper we present the synthesis of enantiopure perhydropyrrolo[3,4-c]pyrazole derivatives by stereoselective intramolecular 1,3-dipolar cycloaddition of azomethine imines with unactivated alkenes positioned on a chiral perhydro-1,3-benzoxazine moiety.

The 3-allyl-2-formylperhydro-1,3-benzoxazines 4a–f were prepared in three steps and good yields from (−)-8-aminomenthol (1) (Scheme 1). Condensation of 1 with the dimer of glycolaldehyde in dichloromethane at room temperature afforded quantitatively the perhydro-1,3-benzoxazine 2 as a single compound which was alkylated with the corresponding allyl bromides and potassium carbonate in refluxing acetonitrile leading to 3a–f. The Swern

Scheme 1
oxidation of alcohols 3a–f leads to aldehydes 4a–f in good yields.

The key step of the synthesis was the intramolecular trapping of the azomethine imines formed in situ by the reaction of 4a–f with \( N,N' \)-disubstituted hydrazines, and the results are summarized in Scheme 2 and Table 1.

As expected, condensation took place at the more basic \( N \)-alkyl- or \( N \)-phenyl substituted nitrogen, rather than at the acyl substituted nitrogen, and the cyclization afforded, with total regioselectivity, the 5,5-fused bicyclic system 5 and 6 and no bridged products.

\( N \)-Acetyl-\( N \)-methylhydrazine reacted much faster than \( N \)-acetyl-\( N \)-phenylhydrazine. The former led to the cyclization products after 4–8 hours of reflux in toluene in excellent yields when reacted with mono- or disubstituted double bonds (entries 1–4), whereas the \( N \)-acetyl-\( N \)-phenyl homolog also yielded the cyclization products in very good yields, but after 34–38 hours of reflux in the same solvent (entries 7 and 9). Interestingly, trisubstituted double bonds in compounds 4e–f also reacted slower than mono- or disubstituted ones, and it was necessary to increase the reaction time to obtain cyclization products in lower yields (entries 5, 6). Finally, due to the lower reactivity of the hydrazine derivative, and the structure of the dipolarophile, the cyclizations of crotyl- 4b and methacrylperhydro-1,3-benzoxazines 4d with \( N \)-acetyl-\( N \)-phenylhydrazine have no synthetic interest because they provided the final products in very low yields (entries 8 and 10). In this case, the long periods of heating allowed the competition of carbonyl-ene cyclization, and these kind of cycloadducts were detected as major products in the final reaction mixtures.

It is worthy to note that in all cases the cycloaddition occurred with complete facial selectivity providing cis-syn adducts as single diastereoisomers, and traces of other cycloadducts were not detected in the \( ^1H \) NMR spectra of the reaction mixtures.

The relative configuration of adducts 5a–f and 6a–d was established by \( ^1H \) NMR, COSY and NOESY experiments. The NOESY contacts point to a cis-fused bicycle with a cis relationship between the substituents \( R_1, R_2 \) and \( H-3a \) and trans for \( H-3b \). On the other hand, the \( ^1H \) NMR signal for the hydrogen \( H-3b \) attached to the \( N,O \)-ketal carbon atom appears as a singlet indicating that the dihedral angle between \( H-3b \) and \( H-3a \) is near to 90° and therefore the substituent attached to the nitrogen atom of the oxazine moiety is in axial arrangement. As an example, Figure 1 shows the NOESY correlations for compound 5e.

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Regio- and Stereoselective Synthesis of Perhydropyrrolo[3,4-c]pyrazole

In summary, a novel totally diastereoselective synthesis of perhydropyrrolo[3,4-c]pyrazole derivatives has been developed by intramolecular [3+2] dipolar cycloaddition. The starting compounds can easily prepared from (–)-8-aminomenthol in three steps, and a variety of different substituents can be introduced into the heterocyclic nucleus depending on the substitution at the double bond and the nature of the hydrazine derivative.

All reactions were carried out in anhydrous solvents under argon in oven-dried glassware. Products were isolated by flash chromatography on silica gel using hexanes–EtOAc (3:1) as elu-

dant.

**Swern Oxidation of Alcohols 4e and 4f; General Procedure**

DMSO (1.8 mL, 25.3 mmol) was added dropwise to a stirred solution of oxalyl chloride (1.0 mL, 11.9 mmol) in CH₂Cl₂ (35 mL) at –78 °C. The mixture was stirred at –78 °C for 15 min, and then a solution of the corresponding alcohol 3e–f (10 mmol) in CH₂Cl₂ (25 mL) was added dropwise via a syringe. After 25 min of additional stirring at –78 °C, Et₃N (7.0 mL, 50 mmol) was added and the reaction was allowed to warm to r.t. After 1 h, the mixture was poured into sat. aq NaHCO₃ solution (40 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 25 mL), the combined organic layers were washed with H₂O, dried and concentrated in vacuo. The residue was chromatographed on silica gel using EtOAc–hexanes (1:30) as eluent.

**Azomethine Imine Generation and 1,3-Dipolar Cycloaddition; General Procedure**

A solution of the appropriate aldehyde 4a–f (2.0 mmol), and acylhydrazine (2.6 mmol) in toluene (40 mL) was refluxed for the time given in Table 1. The solution was concentrated under reduced pressure, and the residue was chromatographed on silica gel using EtOAc–hexanes (1:10) as eluent.
(3aR,3S,4aR,6R,8aS,10aS)-2-Acetyl-3,6,9,9-tetramethyl-dodecahydro-4-oxa-2,3,9a-triazapentaleno[1,2-b]naphthalene
(5a)
Colorless solid; mp 96–97 °C (hexane); [α]D25 –107.2 (c = 1.2, CHCl3).

IR (Nujol): 2923, 1626 cm⁻¹.

1H NMR (CDCl3): δ = 0.84–0.98 (m, 3 H), 0.91 (d, 3 H, J = 6.5 Hz), 1.04 (s, 3 H), 1.05 (s, 3 H), 1.26–1.31 (m, 1 H), 1.35–1.52 (m, 1 H), 1.54–1.57 (m, 1 H), 1.68–1.70 (m, 1 H), 1.83–1.87 (m, 1 H), 2.12 (s, 3 H), 2.53 (s, 3 H), 2.71 (dd, 1 H, J1 = 1.7 Hz, J2 = 8.5 Hz), 2.99–3.07 (m, 3 H), 3.39 (dt, 1 H, J1 = 4.2 Hz, J2 = 10.6 Hz), 4.05 (dd, 1 H, J1 = 1.9 Hz, J2 = 11.8 Hz), 4.63 (s, 1 H).

13C NMR (CDCl3): δ = 19.7, 21.2, 22.0, 24.6, 26.6, 31.1, 34.8, 39.9, 41.2, 43.6, 45.3, 47.5, 50.5, 52.4, 74.4, 76.7, 90.6, 171.7.


(1S,3aR,3S,4aR,6R,8aS,10aS)-2-Acetyl-1,3,6,9,9-pentamethyl-dodecahydro-4-oxa-2,3,9a-triazapentaleno[1,2-b]naphthalene
(5b)
Colorless oil; [α]D25 –95.2 (c = 1.4, CH2Cl2).

IR (film): 2924, 1660 cm⁻¹.

1H NMR (CDCl3): δ = 0.83–1.01 (m, 3 H), 0.91 (d, 3 H, J = 6.5 Hz), 1.04 (s, 3 H), 1.05 (s, 3 H), 1.10–1.33 (m, 1 H), 1.38 (d, 3 H, J = 6.9 Hz), 1.43–1.46 (m, 1 H), 1.52–1.58 (m, 1 H), 1.68–1.70 (m, 1 H), 1.83–1.87 (m, 1 H), 2.11 (s, 3 H), 2.72–2.88 (m, 2 H), 3.22 (dd, 1 H, J1 = 6.2 Hz, J2 = 8.8 Hz), 3.38 (dt, 1 H, J1 = 4.1 Hz, J2 = 10.5 Hz), 3.41 (dd, 1 H, J1 = 8.0 Hz), 4.24 (dq, 1 H, J1 = 3.0 Hz, J2 = 6.9 Hz), 4.61 (s, 1 H).

13C NMR (CDCl3): δ = 20.1, 21.2, 22.0, 23.1, 24.6, 26.6, 31.0, 34.7, 41.2, 43.7, 48.2 (2 C), 49.9, 52.3, 60.5, 74.6, 77.1, 90.6, 171.2.

Anal. Calcd for C20H35N3O2 (345.49): C, 68.02; H, 9.91; N, 12.53. Found: C, 68.16; H, 10.02; N, 12.41.

(1R,3aR,3S,4aR,6R,8aS,10aS)-2-Acetyl-1-phenyl-3,6,9,9-tetramethyl-dodecahydro-4-oxa-2,3,9a-triazapentaleno[1,2-b]-naphthalene
(5c)
Colorless solid; mp 102–104 °C (hexane); [α]D25 –75.9 (c = 1.3, CH2Cl2).

IR (Nujol): 3025, 2922, 1664, 1602, 732, 698 cm⁻¹.

1H NMR (CDCl3): δ = 0.91–1.07 (m, 3 H), 0.92 (d, 3 H, J = 6.5 Hz), 1.09 (s, 3 H), 1.10 (s, 3 H), 1.34–1.40 (m, 1 H), 1.42–1.55 (m, 1 H), 1.57–1.62 (m, 1 H), 1.65–1.71 (m, 1 H), 1.84–1.88 (m, 1 H), 2.25 (s, 3 H), 2.53 (s, 3 H), 3.05–3.08 (m, 1 H), 3.39–3.47 (m, 4 H), 4.74 (s, 1 H), 5.38 (s, 1 H), 7.20–7.25 (m, 5 H).

13C NMR (CDCl3): δ = 20.4, 21.5, 22.1, 24.7, 26.8, 31.1, 34.8, 41.2, 43.8, 47.6, 47.9, 50.8, 52.5, 67.1, 74.8, 77.7, 90.6, 126.5 (2 C), 126.6, 128.1 (2 C), 142.4, 172.6.


(3aR,3S,4aR,6R,8aS,10aS)-2-Acetyl-3,6,9,9-trimethyl-dodecahydro-4-oxa-2,3,9a-triazapentaleno[1,2-b]-naphthalene
(6a)
Colorless solid; mp 191–192 °C (hexane); [α]D25 –12.49 (c = 1.7, CH2Cl2).

IR (Nujol): 2920, 1682, 1595, 759, 696 cm⁻¹.

1H NMR (CDCl3): δ = 0.88–1.05 (m, 3 H), 0.93 (d, 3 H, J = 6.5 Hz), 1.07 (s, 3 H), 1.11 (s, 3 H), 1.38–1.45 (m, 2 H), 1.55–1.58 (m, 1 H), 1.69–1.73 (m, 1 H), 1.91–1.97 (m, 1 H), 2.04 (s, 3 H), 2.78 (d, 1 H, J = 8.2 Hz), 2.96–3.01 (m, 2 H), 3.29 (q, 1 H, J = 8.2 Hz), 3.46 (dt, 1 H, J1 = 4.0 Hz, J2 = 10.5 Hz), 4.10 (d, 1 H, J = 6.8 Hz), 4.36–4.41 (m, 1 H), 4.92 (s, 1 H), 6.92 (s, 1 H, J = 7.3 Hz), 6.95 (d, 2 H, J = 8.1 Hz), 7.26 (dd, 2 H, J1 = 7.3 Hz, J2 = 8.1 Hz).

13C NMR (CDCl3): δ = 20.4, 21.1, 22.1, 24.6, 26.6, 31.1, 34.8, 41.1, 41.7, 42.8, 49.2, 50.4, 52.5, 74.8, 75.1, 90.7, 113.7 (2 C), 121.1, 129.1 (2 C), 149.8, 175.2.

Anal. Calcd for C21H37N3O2 (383.54): C, 72.03; H, 8.67; N, 10.96. Found: C, 72.19; H, 8.56; N, 11.08.

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(1S,3aR,3bS,4aR,6R,8aS,10aS)-2-Acetyl-3-phenyl-1,6,9,9-tetramethyldecahydro-4-oxa-2,3,9a-triazapentaleno[1,2-b]-naphthalene (6b)

Colorless oil; [α]D25 +7.8 (c = 0.8, CH2Cl2).

IR (film): 2920, 1650, 754, 703, 653 cm−1.

1H NMR (CDCl3): δ = 0.86–0.99 (m, 3 H), 0.93 (d, 3 H, J = 6.5 Hz), 0.97–1.02 (d, 3 H, J = 6.9 Hz), 1.06 (s, 3 H), 1.11 (s, 3 H), 1.13–1.33 (m, 1 H), 1.39–1.46 (m, 1 H), 1.5–1.58 (m, 1 H), 1.7–1.79 (m, 1 H), 1.91–1.98 (m, 1 H), 2.02 (s, 3 H), 2.14–2.82 (m, 2 H), 2.38 (t, 1 H, J = 8.3 Hz), 3.46 (dt, 1 H, J1 = 4.0 Hz), 4.80 (q, 1 H, J2 = 10.5 Hz), 5.75 (s, 1 H).

13C NMR (CDCl3): δ = 20.0, 20.9, 21.5, 22.2, 24.8, 26.8, 31.3, 35.0, 41.3, 42.8, 45.0, 50.1, 52.7, 59.1, 73.1, 75.0, 90.8, 112.9 (2 C), 120.3, 129.1 (2 C), 150.7, 176.4.

Anal. Calcd for C24H35N3O2 (397.56): C, 72.51; H, 8.87; N, 10.57.

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References


