CHIRAL FOUR-MEMBERED CYCLIC NITRONES; ASYMMETRIC INDUCTION IN THE (4+2)-CYCLOADDITION REACTION OF CHIRAL YNAMINES AND NITROALKENES

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Abstract. Chiral four-membered cyclic nitrones were synthesized by the asymmetric (4+2)-cycloaddition of nitroalkenes 1 and chiral ynamines 2. The subsequent stereoselective addition of nucleophiles to these nitrones enabled the synthesis of chiral N-hydroxyazetidines.

Asymmetric cycloadditions become increasingly useful in controlling the absolute stereochemistry during the formation of more than one bond in one reaction.1 Previously we have reported the stereoselective synthesis of four-membered cyclic nitrones by the cycloaddition of nitroalkenes 1 and ynamines 2.2 In this reaction two chiral carbon centers are formed of which the stereochemistry at C-2 is determined by the stereochemistry at C-3 in the intermediate nitron ester 3. Upon ring contraction only two enantiomeric nitrones 4 (2R,3R) and 5 (2S,3S) are formed in equal amounts.

We anticipated that a chiral N,N-dialkylamino group in the ynamines 2 might cause asymmetric induction in the cycloaddition with prochiral nitroalkenes, resulting in a preferential formation of one of the enantiomeric nitrones 4 or 5. In this paper we describe the first synthesis of chiral ynamines and their use in the asymmetric synthesis of four-membered cyclic nitrones and 1-hydroxyazetidines.

Scheme 1

The racemic ynamine 2a was synthesized from (+)-2-methylpyrrolidine and 1-ethoxy-1-butyne in analogy with standard procedures3 and was obtained in 61% yield [bp 50-52 °C (5 mm); mass spectrum, m/e 137.120 (M⁺, calcd for C₉H₁₅N: 137.120)]. Similarly, racemic 2,5-dimethyl-1-(phenylethynyl)pyrrolidine (2b) was prepared from the HCl-salt of trans-(+)-2,5-dimethylpyrrolidine4 and (chloroethynyl)benzene in a yield of 16% in analogy with the synthesis of ynamine 2a (Chart 1).

In analogy with the synthesis of compound 2a, the chiral ynamine 2c was obtained from (S)-(−)-2-(methoxymethyl)pyrrolidine and 1-ethoxy-1-butyne in 52% yield ([α]D₂⁵ −47.1 (benzene, c: 1.53); bp 60-62 °C (0.02 mm); mass spectrum, m/e 167.131 (M⁺, calcd for C₁₀H₁₇NO: 167.131)].
Reaction of the lithium salt of (S)-(−)-2-(methoxymethyl)pyrrolidine with (chloroethynyl)benzene afforded the ynamine 2d in 62% yield \([\alpha]_D^{25} -74.3 \) (benzene, c: 1.75); bp 105-108 °C (0.002 mm); mass spectrum, \(m/e\) 215.132 (\(M^+\), calcd for \(C_{14}H_{17}NO: 215.131\)). Both ynamines 2c and 2d were synthesized without racemization in optical yields of more than 95%. 5

When the racemic ynamine 2a was reacted with nitroalkene 1a, two diastereomeric nitrones were isolated in a total yield of 61%, 7 and in a ratio of 66:34. The diastereomers were separated by preparative TLC [aluminum oxide; eluent: chloroform/diethyl ether/petroleum ether bp 40-60 °C 1:1:1 (v/v)] giving a fast eluting fraction [4a; Yield: 41%; \(R_f \approx 0.6\); mp 182-185 °C (chloroform/petroleum ether bp 40-60 °C)] and a slow eluting fraction [5a; Yield: 20%; \(R_f \approx 0.2\); mp 180-182 °C (chloroform/diisopropyl ether)]. Mainly on the basis of the \(^1\)H-NMR absorptions of the methyl groups of the pyrrolidinyl substituent in both isomers we assigned the \((2'R,2R,3R)\)/(2'S,2S,3S) stereochemistry to the racemic nitrone 4a (\(\delta 0.87, \text{bd}, 3\text{H}\)) which is formed in excess and the \((2'R,2S,3S)\)/(2'S,2R,3R) stereochemistry to the isomer 5a (\(\delta 0.82, \text{d}, 3\text{H}\)) (Chart 2).

When racemic ynamine 2b was reacted with nitroalkene 1a, two diastereomeric nitrones were isolated in a yield of 43% (ratio 64:36). 7 The diastereomers were separated by preparative TLC [silica gel; eluent: chloroform/petroleum ether bp 40-60 °C 1:2 (v/v)]. The fast eluting fraction (4d; Yield: 28%; \(R_f \approx 0.5\)) shows in the \(^1\)H-NMR spectrum two doublets at \(\delta 0.89 \) and 0.57 (\(J = 6.3\) Hz, 3H). The slow eluting fraction (5d; Yield: 16%; \(R_f \approx 0\)) shows in the \(^1\)H-NMR spectrum two doublets at \(\delta 0.70 \) and 0.03 (\(J = 6.3\) Hz, 3H) (Chart 2). Molecular models of both possible cis-substituted diastereomeric nitrones 4d and 5d, indicate that in the nitrone with the \((2'R,5'R,2R,3S)\)/(2'S,5'S,2S,3R) stereochemistry only one methyl group of the pyrrolidinyl group may be strongly shielded in the \(^1\)H-NMR spectrum due to shielding by the phenyl group at C-3. Therefore we assigned to the diastereomeric nitrone 4d, which is formed in excess, the \((2'R,5'R,2S,3R)\)/(2'S,5'S,2S,3R) stereochemistry and to the isomer 5d the \((2'R,5'R,2R,3S)\)/(2'S,5'S,2S,3R) stereochemistry.

Reaction of racemic ynamine 2b with nitroalkene 1b gave only one diastereomeric nitrone 5e in a yield of 40% (d.e. > 95% based on NMR spectroscopy). This product shows in the \(^1\)H-NMR spectrum two doublets at \(\delta 0.68 \) and -0.08 (\(J = 6.3\) Hz, 3H) for the methyl groups of the pyrrolidinyl substituent. Reaction of ynamine 2b with nitroalkene 1c also afforded only one diastereomeric nitrone (5f) in a yield of 28% (d.e. > 95% based on NMR spectroscopy). The \(^1\)H-NMR spectrum of 5f exhibits two doublets at \(\delta 0.57 \) and -0.20 (\(J = 6.3\) Hz, 3H) for the methyl groups of the pyrrolidinyl group. On the basis of the large difference of the chemical shifts of the methyl groups in the nitrones 5e and 5f, as was also observed in nitrone 5d, we assigned the \((2'R,5'R,2R,3S)\)/(2'S,5'S,2S,3R) stereochemistry to the nitrones 5e and 5f.
When the optically pure ynamine 2c was reacted with nitroalkene 1a a mixture of two diastereomeric nitrones was isolated in a total yield of 51\% and in a ratio of 73:27. Both diastereomers were separated by preparative TLC (aluminum oxide; eluent: acetone/petroleum ether bp 40-60 °C 3:2 (v/v)), giving a fast eluting fraction [4b; Yield 33\%; [α]_D^{25} +47.8 (chloroform, c: 0.65); R_f - 0.4; mp 177-178 °C (chloroform/diisopropyl ether)] and a slow eluting fraction [5b; Yield: 11\%; [α]_D^{25} -109.1 (chloroform, c: 0.71); R_f - 0.3; mp 170-173 °C (chloroform/diisopropyl ether)] (Chart 2). From molecular models and from comparison of the NMR data with those of the nitrones 4a and 5a we concluded that nitrone which is in a of 46\%, the (2S,2R,3R) stereochemistry and nitrone 5b the (2'S,2S,3S) stereochemistry.

When the optically active ynamine 2d was reacted with nitroalkene 1a for 3 h, two diastereomeric nitrones were isolated in a ratio of 28:68 and in a total yield of 52\%. Separation of the nitrones by column chromatography gave nitrone 4c [Yield: 22\%; [α]_D^{25} -416.7 (chloroform, c: 0.58); mp > 240 °C (chloroform/diisopropyl ether); mass spectrum, m/e 440.209 (M^+, calcd for C_{28}H_{28}N_{2}O_{3}: 440.210)]. We assigned to nitrone 4c, which was formed in a d.e. of 41\%, the (2'S,2S,3R) stereochemistry. Nitrone 5c [Yield 10\%; [α]_D^{25} +304.8 (chloroform, c: 0.836); mp > 240 °C (chloroform/diisopropyl ether); mass spectrum, m/e 440.209 (M^+, calcd for C_{28}H_{28}N_{2}O_{3}: 440.210)] was assigned the (2'S,2R,3S) stereochemistry.

Reaction of racemic nitrone 4a with allylmagnesium bromide, in a mixture of diethyl ether and benzene, gave the allylsubstituted 1-hydroxyazetidine 6a in a yield of 20\% [^{13}C-NMR δ: 170.0 (s, C=O), 77.1 and 74.9 (s, C-4 and C-2); mass spectrum, m/e 404.248 (M^+, calcd for C_{26}H_{32}N_{2}O_{3}: 404.246)]. On the basis of the NMR spectra of corresponding 1-hydroxyazetidines without substituents in the pyrrolidine ring, we assigned the (2'R,2R,3S,4S)/(2'S,2S,3R,4R) stereochemistry to 1-hydroxyazetidine 6a.

When the optically active nitrone 4b was reacted with allylmagnesium bromide 1-hydroxyazetidine 6b was isolated in a yield of 54\%. [[α]_D^{25} = 41.8; (chloroform, c: 1.58); ^{13}C-NMR δ: 170.4 (s, C=O), 76.6 and 74.9 (s, C-4 and C-2); mass spectrum, m/e 434.258 (M^+, calcd for C_{27}H_{34}N_{2}O_{3}: 434.257)] with a stereochemistry as shown in Chart 3.
Finally, when the optically active nitrone 4c was reacted with allylmagnesium bromide, the chiral 1-hydroxyazetidine 6c was obtained in a yield of 31% \([\alpha]_D^{25}+74.6\) (chloroform, c: 0.36); \(1^\text{H}-\text{NMR } \delta: 170.5\) (s, C=O), 80.7 and 76.2 (s, C-4 and C-2); mass spectrum, m/e 482.254 (M\(^+\), calcd for C\(_{31}\)H\(_{34}\)N\(_2\)O\(_3\): 482.257). Comparison of the NMR spectra of 6c with those of related structures, \(^{10}\) shows similar chemical shifts of the characteristic substituents and we assigned the \((2'S,2S,3S,4S)\) stereochemistry to the optically active compound 6c.

![Chart 3](image)

In conclusion we have shown that chiral ynamines are readily available from the corresponding chiral secondary amines and the promising results in the asymmetric \((4+2)\)-cycloaddition reactions with nitroalkenes will be further investigated and extended to other (cyclo)addition reactions of chiral ynamines.

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REFERENCES AND NOTES

6. Hydrolysis of the optically active ynamines gave the corresponding amides (from 2c: \([\alpha]_D^{25} -71.2\) (chloroform, c: 0.66); from 2d: \([\alpha]_D^{25} -48.8\) (chloroform, c: 1.89). The optical rotations corresponded with the rotations of the amides, prepared independently from the corresponding optically active amines and acid chlorides.
7. The isolation of the nitrones in yields lower than 60% is due to the simultaneous formation of unstable \((2+2)\)-cycloadducts. Pennings et al. reported the simultaneous formation of 4-nitrocyclobutenes, as the \((2+2)\)-cycloadducts, in the reaction of ynamines and nitroalkenes (see ref. 2).
11. From previous work it is known that Grignard reagents add stereoselectively from the less hindered side of the four-membered ring: van Elburg, P.A.; Reinhoudt, D.N. Submitted for publication.

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