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**,⁶ 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%; $R_f \sim 0.6$; mp 182-185 °C (chloroform/petroleum ether bp 40-60 °C)] and a slow eluting fraction [**5a**; Yield: 20%; $R_f \sim 0.2$; mp 180-182 °C (chloroform/diisopropyl ether)]. Mainly on the basis of the 1H -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** (δ 0.87, bd, 3H) which is formed in excess and the (2'R,2S,3S)/(2'S,2R,3R) stereochemistry to the isomer **5a** (δ 0.82, d, 3H) (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%; $R_f \sim 0.5$) shows in the 1H -NMR spectrum two doublets at δ 0.89 and 0.57 ($J = 6.3$ Hz, 3H). The slow eluting fraction (**5d**; Yield: 16%; $R_f \sim 0$) shows in the 1H -NMR spectrum two doublets at δ 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 1H -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,2R,3S) 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**⁸ gave only one diastereomeric nitrone (**5e**) in a yield of 40% (d.e. $\geq 95\%$ based on NMR spectroscopy). This product shows in the 1H -NMR spectrum two doublets at δ 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**⁹ also afforded only one diastereomeric nitrone (**5f**) in a yield of 28% (d.e. $\geq 95\%$ based on NMR spectroscopy). The 1H -NMR spectrum of **5f** exhibits two doublets at δ 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**.

Chart 2

- a (2'R,2R,3R)/(2'S,2S,3S) $R^3 = C_2H_5, R^6 = CH_3$
 b (2'S,2R,3R)-(-) $R^3 = C_2H_5, R^6 = CH_2OCH_3$
 c (2'S,2S,3R)-(-) $R^3 = C_6H_5, R^6 = CH_2OCH_3$

- a (2'R,2S,3S)/(2'S,2R,3R)
 b (2'S,2S,3S)-(-)
 c (2'S,2R,3S)-(+)

- (2'R,5'R,2S,3R)/(2'S,5'S,2R,3S) (2'R,5'R,2R,3S)/(2'S,5'S,2S,3R)

- d $R^1 = C_6H_5$
 e $R^1 = H$
 f $R^1 = CH_3$

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%,⁷ 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%; $[\alpha]_D^{25} +47.8$ (chloroform, c: 0.65); $R_f \sim 0.4$; mp 177–178 °C (chloroform/diisopropyl ether)] and a slow eluting fraction [**5b**; Yield: 11%; $[\alpha]_D^{25} -109.1$ (chloroform, c: 0.71); $R_f \sim 0.3$; 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 **4b**, which is formed in a d.e. of 46%, has the (2'S,2R,3R) stereochemistry and that nitrone **5b** has 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%.⁷ Separation of the nitrones by column chromatography gave nitrone **4c** [Yield: 22%; $[\alpha]_D^{25} -416.7$ (chloroform, c: 0.58); mp > 240 °C (chloroform/diisopropyl ether); mass spectrum, m/e 440.209 (M^+ , calcd for $C_{28}H_{28}N_2O_3$: 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%; $[\alpha]_D^{25} +304.8$ (chloroform, c: 0.836); mp > 240 °C (chloroform/diisopropyl ether); mass spectrum, m/e 440.209 (M^+ , calcd for $C_{28}H_{28}N_2O_3$: 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-hydroxyazetidines **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 $C_{26}H_{32}N_2O_2$: 404.246)]. On the basis of the NMR spectra of corresponding 1-hydroxyazetidines without substituents in the pyrrolidine ring,¹⁰ we assigned the (2'R,2R,3S,4S)/(2'S,2S,3R,4R) stereochemistry to 1-hydroxyazetidine **6a**.¹¹

When the optically active nitrone **4b** was reacted with allylmagnesium bromide 1-hydroxyazetidine **6b** was isolated in a yield of 54%. [$[\alpha]_D^{25} -41.8$; (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 $C_{27}H_{34}N_2O_3$: 434.257)] with a stereochemistry as shown in Chart 3.¹¹

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); ^{13}C -NMR δ : 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 $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_3$: 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

a (2'R,2R,3S,4S)/(2'S,2S,3R,4R); $R^3 = \text{C}_2\text{H}_5$, $R^6 = \text{CH}_3$

b (2'S,2R,3S,4S)-(-); $R^3 = \text{C}_2\text{H}_5$, $R^6 = \text{CH}_2\text{OCH}_3$

c (2'S,2S,3S,4S)-(+); $R^3 = \text{C}_6\text{H}_5$, $R^6 = \text{CH}_2\text{OCH}_3$

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.

Acknowledgement. This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO).

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(Received in UK 21 October 1987)