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[3+2] CYCLOADDITION OF DIMETHYL ACETYLENEDICARBOXYLATE, METHYL ACRYLATE, AND ETHYL ACRYLATE TO 4,5-DIHYDRO-5-METHYL-3H-SPIRO[BENZ-2-AZEPINE-3,1'-CYCLOHEXANE] N-OXIDE

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The cycloaddition of methyl acrylate and ethyl acrylate to 4,5-dihydro-5-methyl-3H-spiro[benz-2-azepine-3,1'-cyclohexane] N-oxide proceeds without either regiospecificity or stereospecificity. Eight geometrical isomers of spiro[isoxazolidino[3,2-a]benz-2-azepine-5,1'-cyclohexane] were formed, of which several were isolated as pure samples. The cycloaddition of dimethyl acetylenedicarboxylate proceeds stereoselectively, leading to spiro[isoxazolino[3,2-a]benz-2-azepine-5,1'-cyclohexane] with cis arrangement of the protons at $C_{(7)}$ and $C_{(11b)}$.

Keywords: benz-2-azepines, monosubstituted alkenes, cyclic nitrones, [3+2] cycloaddition.

We have already developed a simple synthesis of 3-substituted and 3-spirofused 4,5-dihydrobenz-2-azepine N-oxides [1, 2], which provides the first opportunity to carry out a systematic study of the [3+2] cycloaddition of alkenes and alkynes to benz-2-azepine nitrones. In particular, acrylonitrile was found to add to 4,5-dihydro-5-methyl-3H-spiro[benz-1-azepine-3,1'-cyclohexane] N-oxide (**1**) without regiospecificity or stereospecificity to give all eight theoretically possible isomers of 1-cyano- and 2-cyanotetrahydro-5H-spiro[isoxazolidino[3,2-*a*]benz-2-azepine-5,1'-cyclohexanes] [3]. On the other hand, the addition of styrene and trimethylvinylsilane to nitrone **1** proceeded regiospecifically to give a ~1:1 mixture of two diastereomers of 2-phenyl- and 2-trimethylsilyltetrahydro-5H-spiro[isoxazolidino[3,2-*a*]benz-2-azepine-5,1'-cyclohexanes] [4, 5]. In the present work, we studied the addition of dimethyl acetylenedicarboxylate, methyl acrylate, and ethyl acrylate to nitrone **1**.

Dimethyl acetylenedicarboxylate adds to nitrone **1** even at 0°C in dichloromethane to give 1,2-dimethoxycarbonyl-7-methyl-4,6,7,11b-tetrahydro-5H-spiro[isoxazolino[3,2-*a*]benz-2-azepine-5,1'-cyclohexane] (**2**). ^{1}H NMR spectroscopy (Table 1) showed that **2** is formed as a ~13:1 mixture of two diastereomers. This conclusion is indicated by finding two signals for H-11b and the methoxy group protons in these spectra. Predominant isomer **2b** was isolated in 63% yield as a pure sample by recrystallization of the reaction mixture.

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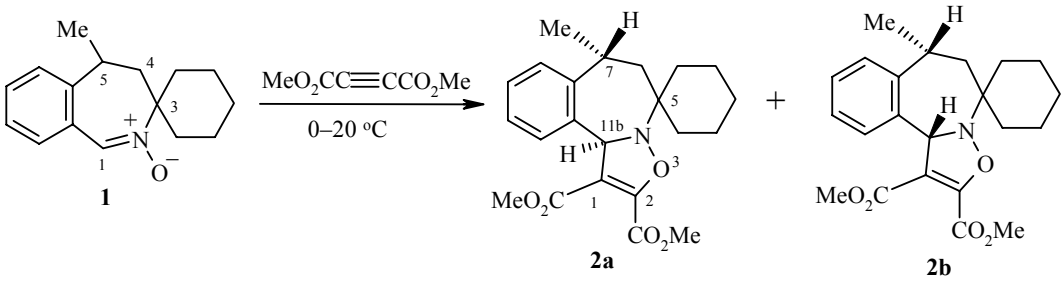
TABLE 1. Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) in the ^{1}H NMR Spectra of Cycloadducts **2-4** in $CDCl_3$ with TMS as Internal Standard

Compound	Protons										
	1A	1B	2A	2B	**6e**	**6a**	**7**	7-Me	11b	C_6H_4	other*[2]
2b	—	—	—	—	2.25 d	1.26 dd	3.31 dq	1.40 d	6.31 s	7.50-7.21 m	3.92 s (CH_3) 3.71 s (CH_3)
3a *trans-trans*	3.55 q	—	4.11 t	4.01 t	2.08 dd	1.42 dd	3.47 m	1.35 d	5.03 d	7.30-7.05 m, 7.28 d	3.79 s (CH_3)
3b *cis-trans*	4.07 q	—	4.18 d	4.18 d	2.19 d	1.25 dd	3.30 m	1.39 d	5.09 d	7.30-7.10 m, 7.37 d	3.75 s (CH_3)
4a *trans-trans*	3.55 q	—	4.13 t	4.01 t	2.08 dd	*	3.47 m	1.37 d	5.03 d	7.30-7.05 m, 7.27 m	4.26 q (CH_2) 1.32 t (CH_3)
4b *trans-cis*	3.14 ddd	2.60 ddd	4.50 dd	—	2.02 dd	*	*	1.30 d	4.73 t	7.25-7.05 m	4.26 q (CH_2) 0.80 t (CH_3)
4c *cis-trans*	4.03 dt	—	4.20-4.10 dd		2.18 d	*	3.30 m	1.38 d	5.09 d	7.40-7.10 m	4.15 q (CH_2) 1.23 t (CH_3)
4d *trans-trans*	3.24 ddd	2.69 ddd	4.58 dd	—	*	*	*	1.37 d	4.71 dd	7.40-7.10 m	4.23 q (CH_2) 1.31 t (CH_3)

Com-pound	Coupling constants												
	1,1	1,2A	1,2B	2,1A	2,1B	1A,11b	1B,11b	2,2	6,6	6e,7	6a,7	7,Me	other
2b	—	—	—	—	—	—	—	—	14.3	0	11.5	6.7	—
3a	—	7.6	7.6	—	—	7.3	—	7.6	14.3	2.1	10.4	7.3	—
3b	—	7.5	7.5	—	—	7.5	—	7.2	14.0	0	11.0	7.0	—
4a	—	7.6	7.6	—	—	7.3	—	7.6	14.4	2.2	*	7.2	7.0 (Et)
4b	12.4	—	—	2.8	9.2	8.6	8.6	—	14.0	3.0	*	7.0	7.0 (Et)
4c	—	7.0	8.0	—	—	8.0	—	11.0	15.0	0	*	7.5	7.1 (Et)
4d	12.0	—	—	2.5	8.5	6.0	10.0	—	14.7	*	*	7.3	7.1 (Et)

* Protons are masked by the signals of other groups. The chemical shift and coupling constant could not be determined.

*[2] The broad multiplet of the cyclohexane ring protons in **2-4** seen at δ ~2.0-1.2 ppm (10H, m, C_6H_{10}).

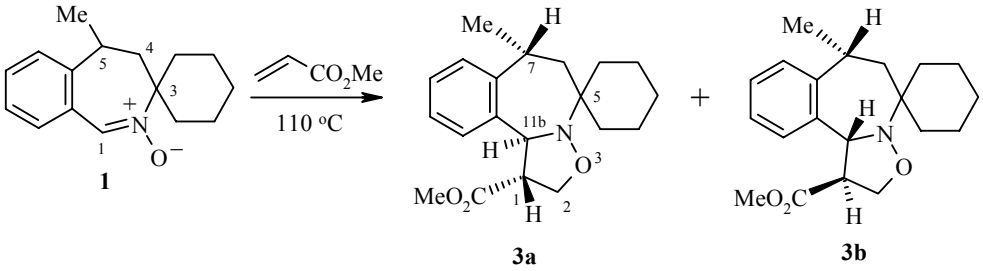


The stereochemistry of adducts **2** was found using the dependence of the $J_{6e,7a}$ coupling constant on the *cis* or *trans* arrangement of H-7 and H-11b of the benz-2-azepine fragment reported in our previous work [1, 6]. The finding of $J_{6a,7a}$ = 11.3 Hz and lack of the corresponding $J_{6e,7a}$ in the spectrum of the major isomer **2b** indicated *cis* arrangement of H-7 and H-11b. In the case of *trans* arrangement of these protons, the value of the $J_{6e,7a}$ coupling constant would have been found in the range 1.5-3.0 Hz. Protons H-7 and H-11b in the minor isomer clearly have *trans* arrangement. Thus, the minor isomer **2a** and major isomer **2b** are formed upon the approach of $MeO_2CC{\equiv}CCO_2Me$ to the nitrone fragment from the *trans* and *cis* position, respectively, relative to the methyl group of N-oxide **1**.

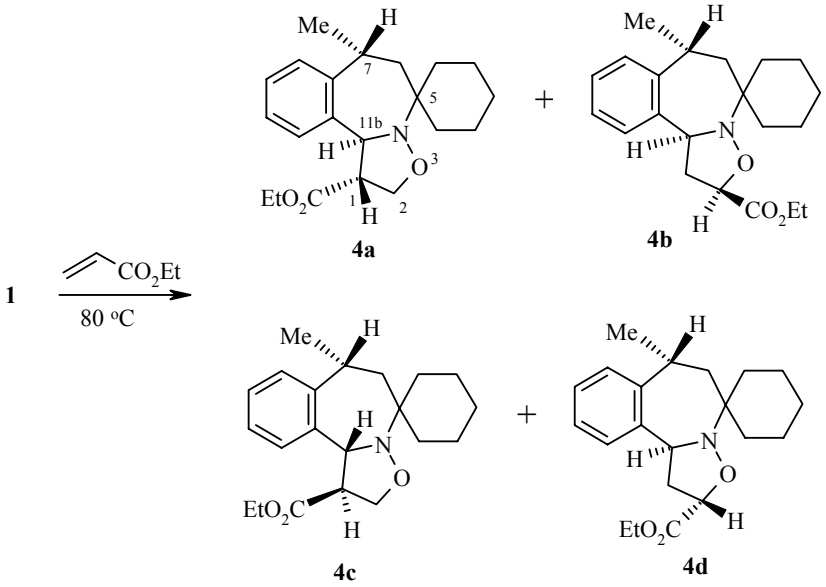
The cycloaddition of methyl acrylate and ethyl acrylate to nitrone **1** was carried out under thermodynamic control at 110°C in toluene and at 80°C in benzene, respectively, in the presence of a ten-fold excess of alkene. The yield of the cycloadduct mixture in both cases was close to quantitative.

The addition of methyl acrylate and ethyl acrylate, similar to the addition of acrylonitrile [3], proceeds without specificity. Analysis of the ^{1}H NMR spectra of the reaction mixtures in the range 5.9-3.3 ppm, featuring the signals for H-1, H-2, H-7, and H-11b, showed that the cycloaddition yields all eight theoretically possible isomers of 1-alkoxycarbonyl- and 2-alkoxycarbonyl-4,6,7,11b-tetrahydro-5H-spiro[isoxazolidino[3,2-*a*]benz-2-azepine-5,1'-cyclohexanes] (**3** and **4**). Since complete chromatographic separation of the reaction mixtures proved impossible, we were unable to obtain a quantitative determination of the composition of these mixtures.

Two isomers of 1-methoxycarbonylisoxazolidino[3,2-*a*]benz-2-azepine, namely **3a** with *trans,trans* orientation of the protons at $C_{(7)}$, $C_{(11b)}$, and $C_{(1)}$ in 15% yield and **3b** with *cis,trans* orientation of these protons in 16% yield, were isolated as pure samples upon chromatography of the reaction mixture in the cycloaddition of methyl acrylate. Both these diastereomers are formed through the *exo*-transition state.



1-Ethoxycarbonylisoxazolidino[3,2-*a*]benz-2-azepine **4a** with *trans,trans* arrangement of protons H-7, H-11b, and H-1 was isolated as a pure sample in 34% yield and 2-ethoxycarbonyl isomer **4b** with *trans,cis* arrangement of these protons was isolated in 7% yield in the [3+2] cycloaddition of ethyl acrylate. Isomer **4a** is formed through an *exo*-transition state, while **4b** is formed through an *endo* transition state. Furthermore, a ~55:45 mixture of adducts **4c** and **4d** was isolated in total yield 23%. Adducts **4c** and **4d** are both formed through an *exo* transition state.



The three-dimensional structure of methoxycarbonyl isomers **3a** and **3b** was established using ^{1}H NMR spectroscopy and the nuclear Overhauser effect for H-1, H-7, and H-11b. Protons H-1 and H-11b in both isomers have *trans* arrangement, while H-7 and H-11b have *trans* arrangement in adduct **3a** but *cis* arrangement in **3b**. We should also note the close similarity of the chemical shift values for the protons in the ^{1}H NMR spectra of isomers **3a** and **3b** (see Table 1) to the shifts of their cyano analogs [3]. The greatest difference in the chemical shifts is found for H-11b: $\Delta\delta$ = 0.15 ppm for isomer **3a** and 0.13 ppm for **3b**. These differences do not exceed 0.08 ppm for the other protons.

The arrangement of H-7, H-11b, and H-1 in 1-ethoxycarbonyl adducts **4a** and **4c** was found by pairwise comparison of the chemical shift and coupling constants as well as the multiplicities of the corresponding ^{1}H NMR signals with those for the methoxycarbonyl (**3a** and **3b**) and nitrile analogs [3]. The greatest chemical shift difference for isomers **3a** and **4a** $\Delta\delta$ = 0.07 ppm is observed for H-1, while $\Delta\delta$ for the other protons does not exceed 0.04 ppm. The chemical shift differences in the spectra of analogs **3b** and **4c** also do not exceed 0.04 ppm. The arrangement of H-7, H-11b, and H-2 in **4b** and **4d** was established analogously. Since the methoxy analogs of these isomers were not isolated, comparison of the ^{1}H NMR spectral data of **4b** and **4d** was carried out with their nitrile analogs [3]. In this case, the chemical shift differences were found to be significantly greater and reached 0.3 ppm for H-1.

In all cases, the $J_{6e,7a}$ coupling constants were taken into account for establishing the arrangement of H-7 and H-11b. This constant varies in the range 1.6-3.0 Hz for *trans* arrangement of these protons but is equal to zero for *cis* arrangement (see Table 1).

Thus, our findings on the regio- and stereoselectivity of the [3+2] cycloaddition of acrylic acid derivatives to benz-2-azepine nitrone **1** are in accord with the results obtained for other cyclic nitrones [7, 8].

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in KBr pellets for crystalline samples and neat for oils. The mass spectra were taken on a Varian MAT-112 mass spectrometer with direct inlet of the sample into the ion source or on an HP MS 5988 GC/MS at 70 eV ionizing voltage. The ^{1}H NMR spectra were taken on a Bruker WP-200 spectrometer at 200 MHz or Bruker WH-400 spectrometer at 400 MHz in $CDCl_3$ solutions at 25°C with TMS as the internal standard. The chemical shifts were measured in ppm on the δ-scale. Silufol

UV-254 plates were used for the thin-layer chromatography with development by iodine vapor. Column chromatography was carried out on Brockmann 0 activity alumina.

1,2-Dimethoxycarbonyl-7-methyl-4,6,7,11b-tetrahydro-5H-spiro[isoxazolino[3,2-*a*]benz-2-azepine-5,1'-cyclohexane] (2). A solution of dimethyl acetylenedicarboxylate (1.50 ml, 12.34 mmol) in dichloromethane (5 ml) was added to a solution of nitrone **1** (3.00 g, 12.34 mmol) in dichloromethane (50 ml) at 0°C. The reaction mixture was maintained at 0°C for 0.5 h and overnight at 20°C. Dichloromethane was distilled off. The residue was recrystallized twice from pentane–ether to give 3.00 (63%) **2** as white crystals, which rapidly turn yellow in the air; mp 115-119°C (dec.), R_f 0.64 (1:2 ethyl acetate–hexane). IR spectrum, ν, cm^{-1}: 1221 (ν_{C-O-C}), 1645 ($\nu_{C=C}$), 1713 and 1759 ($\nu_{C=O}$). Mass spectrum, *m/z* (I_{rel}, %): 385 (M^+, 15), 326 (100), 298 (39), 294 (29), 266 (13), 238 (8), 226 (36), 211 (21), 198 (22), 172 (23), 155 (19), 143 (24), 130 (40), 115 (38), 91 (18), 81 (22), 77 (19). Found, %: C 68.67; H 7.25; N 3.85%. $C_{22}H_{27}NO_5$. Calculated, %: C 68.57; H 7.01; N 3.64; M^+ 385.

1-Methoxycarbonyl-7-methyl-4,6,7,11b-tetrahydro-5H-spiro[isoxazolidino[3,2-*a*]benz-2-azepine-5,1'-cyclohexanes] (3). A mixture of nitrone **1** (2.00 g, 8.20 mmol) and methyl acrylate (7.5 ml, 82 mmol) in toluene (70 ml) was heated at reflux for 20 h with monitoring by thin-layer chromatography. Toluene and excess methyl acrylate were distilled off in vacuum. The residue was subjected to chromatography on a 55×1.5-cm alumina column with 1:30 ethyl acetate–hexane as the eluent. The following pure samples were isolated.

Spiro Product 3a was obtained in 14.8% yield (0.40 g) as a yellow oil, R_f 0.55 (1:4 ethyl acetate–hexane). IR spectrum, ν, cm^{-1}: 1735 ($\nu_{C=O}$). Mass spectrum, *m/z* (I_{rel}, %): 329 (M^+, 86), 314 (25), 300 (15), 286 (100), 273 (6), 270 (30), 256 (6), 240 (11), 226 (36), 218 (21), 202 (15), 172 (9), 156 (9), 143 (59), 129 (41), 115 (20), 97 (53), 82 (30), 54 (33), 40 (32). Found, %: C 73.12; H 8.49; N 4.10. $C_{20}H_{27}NO_3$. Calculated, %: C 72.94; H 8.26; N 4.25; M^+ 329.

Spiro Product 3b was obtained in 16.3% yield (0.44 g) as white crystals, mp 84-86°C (hexane), *Rf* 0.38 (1:4 ethyl acetate–hexane). IR spectrum, ν, cm^{-1}: 1738 ($\nu_{C=O}$). Mass spectrum, *m/z* (I_{rel}, %): 329 (M^+, 73), 314 (13), 300 (43), 286 (100), 273 (8), 256 (2), 240 (4), 226 (15), 172 (5), 143 (14), 129 (17), 115 (9), 97 (8), 82 (9), 54 (13), 40 (12). Found, %: C 73.19; H 8.33; N 4.15. $C_{20}H_{27}NO_3$. Calculated, %: C 72.94; H 8.26; N 4.25; M^+ 329.

1- and 2-Ethoxycarbonyl-7-methyl-4,6,7,11b-tetrahydro-5H-spiro[isoxazolino[3,2-*a*]benz-2-azepine-5,1'-cyclohexanes] (4). A mixture of nitrone **1** (0.50 g, 2.00 mmol) and ethyl acrylate (2.00 g, 20 mmol) in benzene (10 ml) was heated at reflux for 10 h with monitoring by thin-layer chromatography. Benzene and excess ethyl acrylate were distilled off in vacuum. The residue was subjected to chromatography on a 40×1.5-cm alumina column with 1:5 ethyl acetate–petroleum ether as the eluent. The following compounds were separated.

Spiro Product 4a was obtained in 34% yield (0.23 g) as white crystals; mp 90-91°C (from hexane), R_f 0.75 (1:4 ethyl acetate–petroleum ether). IR spectrum, ν, cm^{-1}: 1731 ($\nu_{C=O}$). Mass spectrum, *m/z* (I_{rel}, %): 343 (M^+, 79), 328 (26), 314 (16), 300 (100), 287 (4), 270 (16), 240 (4), 232 (25), 226 (42), 216 (10), 196 (5), 184 (7), 172 (9), 156 (8), 143 (51), 129 (34), 115 (16), 98 (38), 91 (12), 77 (11), 55 (46). Found, %: C 73.22; H 8.61; N 4.00. $C_{21}H_{29}NO_3$. Calculated, %: C 73.47; H 8.45; N 4.08; M^+ 343.

Spiro Product 4b was obtained in 7% yield (0.05 g) as a light yellow oil, R_f 0.60 (1:4 ethyl acetate–petroleum ether). IR spectrum, ν, cm^{-1}: 1733 ($\nu_{C=O}$). Mass spectrum, *m/z* (I_{rel}, %): 343 (M^+, 70), 328 (26), 314 (10), 300 (100), 287 (6), 270 (16), 271 (7), 232 (38), 226 (50), 224 (12), 216 (7), 172 (9), 156 (8), 143 (39), 129 (39), 115 (18), 113 (12), 98 (31), 91 (19), 77 (11), 55 (40).

Mixture of Isomers 4c and 4d was obtained in 23% yield (0.16 g) as a mixture of ~55% **4c** and 45% **4d**, white crystals; mp 73-75°C (hexane), R_f 0.42-45 (1:4 ethyl acetate–petroleum ether). IR spectrum, ν, cm^{-1}: 1730 ($\nu_{C=O}$). Mass spectrum, *m/z* (I_{rel}, %): 343 (M^+, 36), 328 (7), 314 (6), 300 (36), 270 (24), 243 (26), 226 (100), 211 (10), 184 (11), 172 (5), 143 (30), 132 (61), 115 (18), 98 (28), 91 (15), 77 (18), 67 (8), 55 (59). Found, %: N 4.05. $C_{21}H_{29}NO_3$. Calculated, %: N 4.08%; M^+ 343.

The total yield of all cycloadducts **4** after column chromatography was 78%.

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