A Regioselective Route to 3-Alkyl-1-aryl-1*H*-pyrazole-5-carboxylates: Synthetic Studies and Structural Assignments

Wallace T. Ashton*

Department of Exploratory Chemistry,
Merck Research Laboratories, P.O. Box 2000,
Rahway, New Jersey 07065

George A. Doss

Department of Animal and Exploratory Drug Metabolism,
Merck Research Laboratories, P.O. Box 2000,
Rahway, New Jersey 07065

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Ethyl 2,4-dioxooctanoate (**1**) was selectively protected as the 2-(methoxyimino) derivative **2**. When **2** was reacted with phenylhydrazine hydrochloride, ethyl 3-butyl-1-phenyl-1*H*-pyrazole-5-carboxylate (**4**) was favored over the corresponding 5-butyl-1-phenyl-1*H*-pyrazole-3-carboxylate product **5** by a ratio of at least 6:1, a complete reversal of the regioselectivity observed for **1**. The structures of **4** and **5** were assigned definitively by NOE difference experiments. Regiochemical and configurational assignments of the mono- and bis(methoxyimino) derivatives of **1** were also achieved by 1D and 2D ^{1}H and ^{13}C nmr methods.

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Introduction.

As part of a synthetic program aimed at nonpeptide angiotensin II antagonists, we required an efficient route to 3-alkyl-1-aryl-1*H*-pyrazole-5-carboxylic acid derivatives. An obvious possibility was the reaction of 2,4-diketo esters with arylhydrazines. In general, however, this reaction has been reported to give predominantly the isomeric 1*H*-pyrazole-3-carboxylates [1-5]. A further complication was the lack of conclusive structural assignments, apart from an instance in which the pyrazolecarboxylate isomers could be correlated with known compounds by chemical degradation [3]. That the 1*H*-pyrazole-3-carboxylate should be favored is not surprising, as this would result from initial attack of the more nucleophilic nitrogen of the arylhydrazine at the more electrophilic 2-carbonyl of the diketo ester. Such a rationale has been applied to the regioselective conversion of 2,4-diketo esters to 5-substituted-isoxazole-3-carboxylates upon reaction with hydroxylamine hydrochloride [6,7].

Scheme I

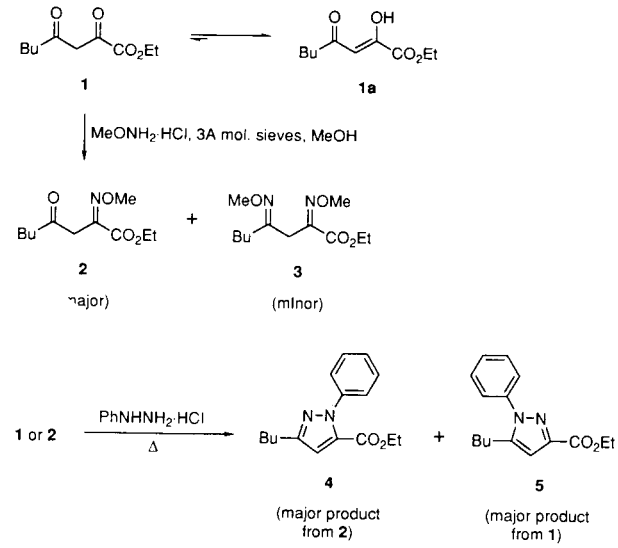


Table I

Conversion of 1 and 2 to Pyrazoles 4 and 5

Entry	Starting Material	Phenylhydrazine Form	Phenylhydrazine Equivalents	Solvent	Temperature (°C)	Time (hours)	Product Ratio (**4**:**5**) [a]
1	**1**	free base	1	EtOH	80	3	1:3-1:4
2	**1**	HCl salt	1	AcOH	85	0.5	1:≥10
3	**1**	HCl salt	1.2	2:1 AcOH-2methoxyethanol	85	1	1:4.7 [b]
4	**2**	free base	1-1.1	EtOH	80	2-5	– [c]
5	**2**	HCl salt	1	AcOH	110	0.2	≥10:1
6	**2**	HCl salt	1	EtOH	80	16	≥10:1
7	**2**	HCl salt	2	2:1 AcOH-2methoxyethanol	105	5	6.4:1 [b]
8	**2**	free base	1.1	AcOH	80	3	[d]

[a] Ratio estimated by nmr and tlc except as indicated. [b] Ratio of isolated products. [c] Unstable, non-pyrazole products formed; only traces of **4** detected. [d] Ratio similar to entry **7** by tlc but not as clean.

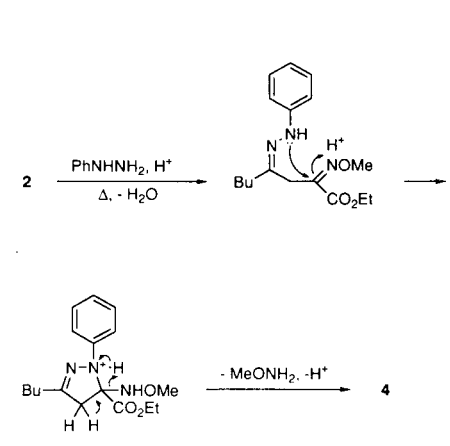
In order to achieve a regioselective synthesis of 1*H*-pyrazole-5-carboxylates from 2,4-diketo esters, it would thus be necessary to protect the 2-carbonyl in order to direct initial attack of the arylhydrazine to the 4-carbonyl. We hoped to take advantage of the greater electrophilicity of the 2-carbonyl for selective protection. Ideally, the protecting group, although resistant to arylhydrazine attack relative to the 4-carbonyl, could be displaced subsequently by the proximate 4-(arylhydrazone) NH to give the pyrazolecarboxylate without the necessity of separate deprotection and cyclization steps. Our candidate protecting group was the *O*-methyloxime. The goal, therefore, was to evaluate the reactions of phenylhydrazine with a model 2,4-diketo ester and its 2-(methoxyimino) derivative and to assign definitively the structures of the pyrazole products as well as key intermediates.

Results and Discussion.

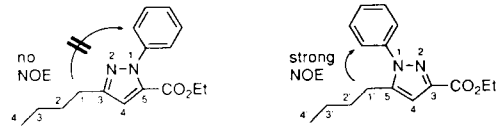
The model diketo ester **1** [2,8], prepared from 2-hexanone and diethyl oxalate, was reacted (Scheme I) with methoxylamine hydrochloride in the presence of molecular sieves [9] to give a single mono(methoxyimino) derivative **2** as well as a small amount of bis(methoxyimino) product **3** (structural assignments discussed below). Next, the reactions of **1** and **2** with phenylhydrazine were studied (Table I). In accord with expectations, the diketo ester **1**, upon heating with phenylhydrazine either as the free base or the hydrochloride salt, gave a mixture of pyrazole products favoring the 1-phenyl-1*H*-pyrazole-3-carboxylate **5** over the corresponding 5-carboxylate **4** by ratios varying from at least 3:1 to more than 10:1 (structural assignments discussed below).

Similar attempts to react the methoxime derivative **2** with phenylhydrazine free base were not encouraging, as only traces of **4** could be detected by tlc. The starting material **2** was consumed, but the two major products (observed as a close pair of spots on tlc with R_f values intermediate between those of **4** and **5**) were unstable to attempted isolation and could not be characterized. Additional heating time under these conditions did not lead to a significant increase in the small amount of **4**. In contrast, reaction of **2** with phenylhydrazine hydrochloride in either acetic acid or ethanol gave almost complete conversion to pyrazolecarboxylate products (Scheme I), with **4** favored over **5** by at least a 10:1 ratio on the basis of nmr, a dramatic reversal of the regioselectivity compared to **1**. For follow-up studies, a 2:1 mixture of acetic acid and 2-methoxyethanol was adopted as the solvent system in order to improve the solubility of the phenylhydrazine hydrochloride and minimize byproducts. Under these conditions, with 2 equivalents of phenylhydrazine hydrochloride used to ensure complete reaction, the ratio of **4**:**5** on the basis of isolated yields was 6.4:1 from **2**, whereas a ratio of 1:4.7 was obtained from **1** in a similar run. Having established the importance of acid in the pyrazolecarboxylate formation from **2**, it was found that phenylhydrazine free base could substitute for the hydrochloride when acetic acid replaced ethanol as solvent. However, the reaction was not as free of side products. A possible mechanism (Scheme II) for the synthesis of **4** from **2** entails initial formation of the phenylhydrazone at C-4 followed by ring closure and elimination of methoxylamine. The role of the acid catalyst may be in activating C-2 to neighboring group nucleophilic attack by protonation of the methoxime and/or in assisting the departure of methoxylamine.

Scheme II



Unequivocal structural assignments of the regioisomers **4** and **5** were made on the basis of nuclear Overhauser effect (NOE) difference spectroscopy. Irradiation of the butyl CH_2 adjacent to the ring strongly enhanced phenyl proton signals in **5**, whereas no corresponding enhancement was observed for **4**. This clearly established **5** as the 1-phenyl-1*H*-pyrazole-3-carboxylate, in which the phenyl group is adjacent to the butyl side chain, and **4** as the 1-phenyl-1*H*-pyrazole-5-carboxylate.



4 **5**

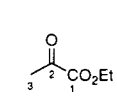
Structural properties of intermediates **1**-**3** were also determined with the aid of nmr methods. By nmr, **1** appeared to be completely in the enolized form **1a** (evidenced by a one-proton singlet at 6.35 ppm, attributed to the proton at C-3). In contrast, **2** and **3** showed no evidence of enolic character (two-proton singlets at 3.68 and 3.43/3.44, respectively, corresponding to the methylene group at the 3-position). The methoxime **2** appeared to be a single syn or anti isomer, whereas the bis(methoxime) **3**, although homogeneous by tlc, showed two sets of nmr signals, suggesting the presence of one syn-anti pair

in nearly a 1:1 ratio. Spectral evidence confirmed the 2-position rather than the 4-position as the site of the methoxime group in **2**. The chemical shift of the protons at C-5 was essentially unchanged in **2** compared to **1**, whereas in **3** the corresponding two-proton triplet was shifted upfield by 0.21 and 0.29 ppm for the two isomers relative to **1**. This is consistent with the location of the second methoxime group in **3** (*i.e.*, the one not present in **2**) at the 4-position. Furthermore, the ^{13}C signals of **2** and **3** were assigned by a ^{13}C-^{1}H correlation (HETCOR) experiment [10,11]. The major difference between the mono- and bis-(methoxime) was in the chemical shift at C-5, not C-1, confirming the presence of the methoxime group at the 4-position in **3** but not in **2**.

Stereochemical assignments of the syn-anti isomers of **3** were made as follows. From the ^{13}C nmr spectrum of **3**, it was apparent that the major chemical shift differences between the two isomers were at C-5 ($\Delta\delta \approx 6$ ppm) and at C-3 ($\Delta\delta \approx 3$ ppm), indicating that the site of syn-anti isomerism is at the 4-methoxime and not at the 2-methoxime. Such shifts at the adjacent positions would be expected on the basis of the fact that in oximes (and related derivatives), the syn carbon is shielded by approximately 4-9 ppm compared to the anti carbon [12].

Surprisingly little precedent could be found in the literature to support a rigorous configurational assignment of the 2-methoxime in **2** and **3**. In the case of some 2-(methoxyimino)-2-(4-thiazolyl)acetic acid esters, both the syn and anti methoximes could be obtained, with the *E* isomer (anti with respect to the ester) being favored under equilibrating conditions [13]. However, the nmr determinations hinged on the chemical shift of a thiazole ring proton and could not be applied to the present compounds. A 2-(methoxyimino)-2-(2-pyridyl)acetic acid derivative has been claimed to exist as the *Z* isomer [14], but in that case hydrogen bonding from the free acid to the oxygen of the methoxyimino group could stabilize the *Z* (syn) configuration.

In the absence of both isomers, it was impossible to determine the configuration of the 2-methoxime in **2** or **3** on the basis of ^{13}C chemical shifts alone. Attempts to infer the configuration from NOE difference experiments were also unsuccessful. In an effort to resolve this question, the *O*-methyloxime **7** prepared from ethyl pyruvate (**6**) was studied as a model compound. The corresponding methyl ester [15] and benzyl ester [16] have been reported, but the methoxime stereochemistry was not determined. Compound **7** too was a single isomer, and the configuration of the 2-methoxime in **2**, **3**, and **7** appeared to be identical based on the close similarity of the ^{13}C chemical shift of C-1 in the three compounds. An unambiguous assignment of the stereochemistry in **7** could be made on the basis of the nmr correlations of Krivdin and coworkers [17], who demonstrated that the one-bond ^{13}C-^{13}C coupling constant ($^{1}J_{CC}$) between the oxime carbon and the anti α-carbon is larger than that in the corresponding ketone by approximately 8-11 Hz. The $^{1}J_{CC}$ values for ethyl pyruvate (**6**) and its methoxime **7**, determined by means of the 1D INADEQUATE nmr technique [18] and shown in Table II, were consistent only with the *E* (anti) configuration of the methoxime in **7**. A similar comparison of $^{1}J_{CC}$ values between **2** and **1** was not applicable because of the enolic character of **1**. However, the $^{1}J_{CC}$ values for **2** (Table II) closely corresponded to those for **7**. Thus the methoxime configuration in **2** can also be assigned as *E*, and by analogy this can be extended to the configuration of the 2-methoxime in **3**.



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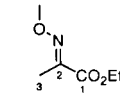
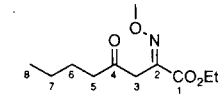
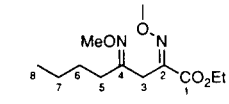


7 (E-oxime)



2 (E-oxime)



3 (2-E, 4-E,Z)

Table II

Selected $^{1}J_{CC}$ Values (Hz) for Compounds 2,6, and 7

$^{1}J_{CC}$	**6**	**7**	**2**
C^1-C^2	67.4	81.0	83.7
C^2-C^3	43.6	43.2	45.7

Conclusions.

A highly regioselective route to 1-aryl-1*H*-pyrazole-5-carboxylates has been realized. The key to the approach is selective protection of a 2,4-diketo ester as the 2-methoxime, which blocks initial attack of arylhydrazine at C-2 but still allows ring closure of a postulated 4-(arylhydrazone) intermediate. A combination of ^{1}H and ^{13}C nmr techniques has allowed definitive structural characterization of the regioisomeric pyrazole products and their intermediates. This synthetic route has recently been adapted to prepare a series of 1,3,4-trisubstituted-1*H*-pyrazole-5-carboxylates [19].

EXPERIMENTAL

Ethanol was dried over 3A molecular sieves. The ^{1}H and ^{13}C nmr spectra were recorded on Varian XL-300, XL-400, Unity 400 or VXR 500 spectrometers and are reported as ppm downfield relative to tetramethylsilane. The ^{13}C nmr spectra were ac-

quired at 125 MHz and were referenced to the deuteriochloroform signal at 77.0 ppm. Positive ion fast atom bombardment (FAB) or electron impact (EI) mass spectra were obtained on Varian MAT 731 or MAT 212 instruments. Column chromatography was carried out on E. Merck silica gel 60 (70-230 mesh). All compounds were homogeneous by tlc on Analtech silica gel GF plates in the indicated solvent system. Elemental combustion analyses were performed by Robertson Microlit Laboratories, Madison, NJ.

Ethyl 2,4-Dioxooctanoate (**1**).

This material [8] was prepared from 2-hexanone and diethyl oxalate in the presence of sodium ethoxide in ethanol by the method of Seki and coworkers [2], with a modified work-up. After 5 hours at 60°, the mixture was cooled and concentrated. The residue was partitioned between ether and cold dilute hydrochloric acid. The organic phase was washed with water, dried over magnesium sulfate, filtered and evaporated *in vacuo* at ≤40° to give an 82% yield of light yellow-orange oil, suitable for use without further purification, existing exclusively in enolic form by nmr; tlc in 95:5:0.1 dichloromethane-methanol-acetic acid; ^{1}H nmr (300 MHz, deuteriochloroform): δ 0.91 (t, J = 7.5 Hz, 3H, C^8H_3), 1.2-1.4 (m, 5H) including 1.36 (t, J = 7 Hz, 3H, OCH_2CH_3), 1.62 (m, 2H, C^6H_2), 2.47 (t, J = 7.5 Hz, 2H, C^5H_2), 4.33 (q, J = 7 Hz, 2H, OCH_2CH_3), 6.35 (s, 1H, C^3H).

Ethyl 2-Methoxyimino-4-oxooctanoate (**2**).

A mixture of 7.00 g (35 mmoles) of **1**, 3.07 g (36.75 mmoles) of methoxylamine hydrochloride, 35 g of 3A molecular sieves, and 35 ml of dry ethanol was stirred vigorously at room temperature in a stoppered flask for 21.5 hours. The mixture was filtered, and the filter cake was washed with ethanol. The combined filtrate and washings were concentrated *in vacuo* at ≤35°, and the residue was partitioned between ether and saturated sodium bicarbonate solution. The ether layer was washed twice with water, dried over magnesium sulfate and filtered. Concentration *in vacuo* at ≤30° gave a reddish-orange oil, which was column chromatographed twice (gradient elution, first with 3-7.5% and then 3-10% ethyl acetate in hexane) to yield, after vacuum-drying at room temperature, 4.14 g (52%) of **2** as a very pale yellow oil; tlc in 4:1 hexane-ethyl acetate; ^{1}H nmr (400 MHz, deuteriochloroform): δ 0.88 (t, J = 7.1 Hz, 3H, C^8H_3), 1.2-1.35 (m, 5H, C^7H_2, OCH_2CH_3), 1.54 (m, 2H, C^6H_2), 2.45 (t, J = 7.3 Hz, 2H, C^5H_2), 3.68 (s, 2H, C^3H_2), 4.03 (s, 3H, OCH_3), 4.31 (q, J = 6.8 Hz, 2H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 13.8 (C-8), 14.2 (OCH_2CH_3), 22.2 (C-7), 25.8 (C-6), 39.4 (C-3), 42.4 (C-5), 62.1 (OCH_2CH_3), 63.5 (OCH_3), 146.6 (C-2), 163.0 (C-1), 204.1 (C-4); ms: (FAB) m/z 230 (MH^+).

Anal. Calcd. for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.65; H, 8.05; N, 6.05.

Ethyl 2,4-Bis(methoxyimino)octanoate (**3**).

In a preparation of **2** similar to that above, the higher R_f impurity (eluted ahead of **2** upon column chromatography) was isolated in 8% yield as a pale yellow oil corresponding to **3**, which by nmr appeared to exist as a mixture of syn and anti isomers in nearly a 1:1 ratio; tlc in 9:1 hexane-ethyl acetate; ^{1}H nmr (300 MHz, deuteriochloroform): δ 0.88, 0.89 (overlapping t, J = 7.5 Hz, total 3H, C^8H_3), 1.2-1.35 (m, 5H, C^7H_2, OCH_2CH_3), 1.45 (m, 2H, C^6H_2), 2.18, 2.26 (t, J = 7.5 Hz, total 2H, C^5H_2), 3.43, 3.44 (overlapping s, total 2H, C^3H_2), 3.74, 3.75 (overlapping s, total 3H, OCH_3), 4.02, 4.04 (overlapping s, total 3H, OCH_3), 4.31, 4.32 (overlapping q, J = 7.5 Hz, total 2H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 13.82 and 13.84 (C-8), 14.17 and 14.23 (OCH_2CH_3), 22.38 and 22.73 (C-7), 26.73 (C-3 of 4*Z* isomer), 28.21 (C-5 of 4*E* isomer), 27.79 and 28.58 (C-6), 29.83 (C-3 of 4*E* isomer), 34.06 (C-5 of 4*Z* isomer), 61.15 and 61.33 (OCH_3), 61.79 and 61.91 (OCH_2CH_3), 63.18 and 63.23 (OCH_3), 148.38 and 148.63 (C-2), 155.44 and 156.11 (C-4), 163.15 and 163.18 (C-1); ms: (FAB) m/z 259 (MH^+).

Anal. Calcd. for $C_{12}H_{22}N_2O_4 \cdot 0.1CH_2Cl_2$: C, 54.47; H, 8.39; N, 10.50. Found: C, 54.83; H, 8.04; N, 9.99 [20].

Ethyl 3-Butyl-1-phenyl-1*H*-pyrazole-5-carboxylate (**4**).

A mixture of 50.4 mg (0.22 mmole) of **2**, 63.8 mg (0.44 mmole) of phenylhydrazine hydrochloride, 0.5 ml of glacial acetic acid and 0.25 ml of 2-methoxyethanol was stirred under nitrogen at 105° for 5 hours. The resulting solution was cooled, resulting in considerable crystallization. The mixture was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and 0.2 *N* hydrochloric acid. The organic phase was washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography of the residue (elution with 95:5 and then 90:10 hexane-ethyl acetate) initially afforded 46.2 mg (77%) of **4** as a very light orange oil; homogeneous by tlc in 9:1 hexane-ethyl acetate (R_f 0.5); ^{1}H nmr (400 MHz, deuteriochloroform): δ 0.93 (t, J = 7.3 Hz, 3H, $C^{4'}H_3$), 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.39 (m, 2H, $C^{3'}H_2$), 1.66 (m, 2H, $C^{2'}H_2$), 2.68 (t, J = 7.7 Hz, 2H, $C^{1'}H_2$), 4.20 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.81 (s, 1H, pyrazole H-4), 7.35-7.45 (m, 5H, C_6H_5); ms: (FAB) m/z 273 (MH^+).

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.59; H, 7.58; N, 10.02.

Subsequently eluted was 7.4 mg (12%) of the isomer **5**, which was identical by nmr and tlc to that prepared as described below.

Ethyl 5-Butyl-1-phenyl-1*H*-pyrazole-3-carboxylate (**5**).

To 100 mg (0.5 mmole) of **1** were added 87 mg (0.6 mmole) of phenylhydrazine hydrochloride, 1 ml of glacial acetic acid, and 0.5 ml of 2-methoxyethanol. The mixture was stirred at 85° for 1 hour and then worked up and chromatographed as described above for **4**. Initially eluted was 16.8 mg (12%) of **4**, identical by tlc and nmr to that prepared as described above. Subsequently eluted was 79.3 mg (58%) of **5** as a very pale golden, viscous oil; tlc in 9:1 hexane-ethyl acetate (R_f 0.3); ^{1}H nmr (400 MHz, deuteriochloroform): δ 0.84 (t, J = 7.4 Hz, 3H, $C^{4'}H_3$), 1.29 (m, 2H, $C^{3'}H_2$), 1.38 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.55 (m, 2H, $C^{2'}H_2$), 2.59 (t, J = 7.7 Hz, 2H, $C^{1'}H_2$), 4.39 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.74 (s, 1H, pyrazole H-4), 7.35-7.5 (m, 5H, C_6H_5); ms: (FAB) m/z 273 (MH^+).

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.55; H, 7.37; N, 10.07.

Ethyl Pyruvate *O*-Methyloxime (**7**).

This material was obtained from ethyl pyruvate (**6**) by the method used to prepare **2** except that an excess (1.5 equivalents) of methoxylamine hydrochloride was used, and the mixture was worked up after 2 hours. Column chromatography on silica gel (elution with 4:1 and then 2:1 petroleum ether-dichloromethane) gave a 43% yield of very pale yellow oil; tlc in 9:1 hexane-ethyl acetate; ^{1}H nmr (400 MHz, deuteriochloroform): δ 1.33 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.02 (s, 3H, $CH_3C{=}N$), 4.04 (s, 3H, OCH_3),

4.31 (q, J = 7.1 Hz, 2H, OCH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 11.1 (C-3), 14.0 (OCH_2CH_3), 61.6 (OCH_2CH_3), 62.9 (OCH_3), 148.9 (C-2), 163.6 (C-1); ms: (EI) m/z 145 (M^+).

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.49; H, 7.51; N, 9.48.

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[20] This was the best value obtainable for N.