# AMINOALKYLATION OF ALDEHYDES WITH GLYOXAL N,N-DIMETHYLMONOHYDRAZONE YIELDS STABLE 4-SUBSTITUTED PYRROLIN-3-ONES

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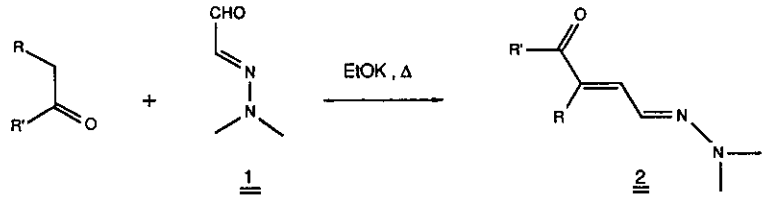
Abstract - Aminoalkylation reaction of various enolizable aldehydes with glyoxal N,N-dimethylmonohydrazone led to 4-substituted 1-N,N-dimethyl-3-morpholinopyrroles 3, which are easily hydrolyzed to novel pyrrolin-3-ones 5.

In continuation of previous studies on aldol condensations[1] and aminoalkylation reactions[2] involving glyoxylic acid, we became interested in the use of glyoxal as monofunctional reagent. Generally glyoxal is used as difunctional reagent, for example in cycloaddition or polycondensation reactions[3]. Recently the monoacetal of glyoxal described[4]. On the other hand Severin and Poehlmann described the N,N-dimethylhydrazone of glyoxal 1[5] and used it in aldol condensations such as the preparation of β-acylacrolein N,N-dimethylhydrazones 2 (scheme 1).



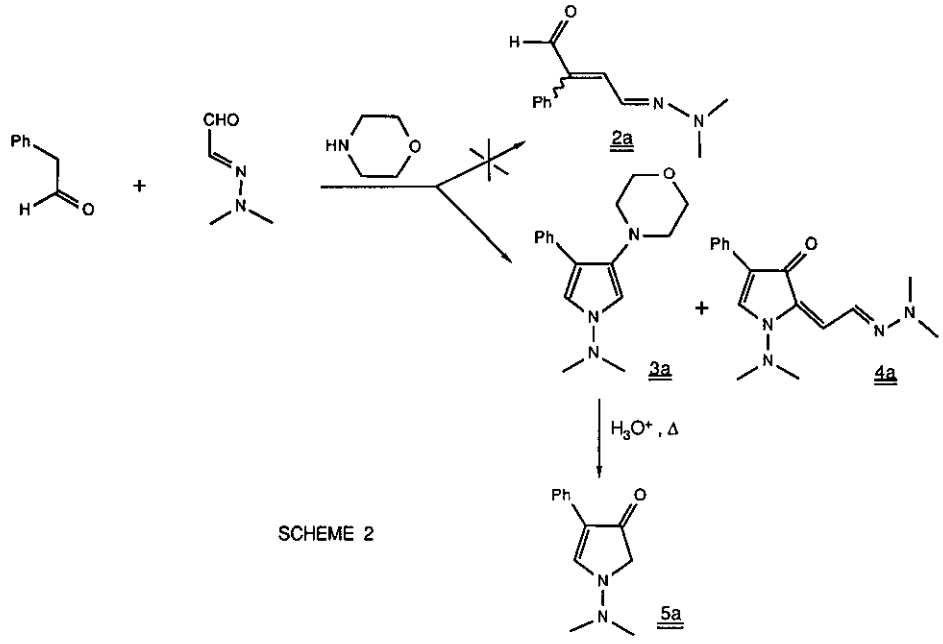

1 2

| | R | R' |
|---|---|---|
| a | Ph | H |
| b | Me | H |
| c | i-Pr | H |
| d | H | Ph |

SCHEME 1

In this paper we report the results obtained when the N,N-dimethylhydrazone of glyoxal was used in Mannich reactions.

When acetophenone was reacted with 1 in the presence of two equivalents of morpholine, the expected β-benzoylacrolein 2d (R=H, R'=Ph) was obtained in satisfactory yields. Surprisingly, when phenylacetaldehyde was used instead of acetophenone, the reaction did not afford the corresponding β-formylacrolein 2a (R=Ph, R'=H), but gave rise to a mixture of two pyrrolic derivatives 3a and 4a, as shown in Scheme 2.




SCHEME 2

The structures of the compounds 3a and 4a were identified by ir, $^{1}H$- and $^{13}C$-nmr spectroscopy. Mass spectra and further chemical transformations were consistent with the proposed structures.

Thus the 2-alkylidenepyrrolin-3-one 4a shows by ir analysis a typical absorption at 1665 $cm^{-1}$ and by $^{13}C$-nmr a signal at 165 ppm for the carbonyl group, whereas the enamine character of the substituted 3-morpholinopyrrole 3a was illustrated by its hydrolysis in acidic medium to the corresponding pyrrolin-3-one 5a. These unexpected results prompted us to further investigations, using different enolizable aldehydes under various experimental conditions (temperature, amounts of morpholine). Data are summarized in Table 1.

| Run | Aldehyde (R) | Equivalents of morpholine | Temp (°C) | Composition of the reaction mixture 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| a | Ph | 0.3 | 5 | nd[a)] | 15 | 85 |
| | | 1 | 25 | nd | 42 | 58 |
| | | 2 | 25 | nd | 59 | 41 |
| | | 3 | 25 | nd | 70 | 30 |
| | | 10 | 75 | nd | 80 | 20 |
| b | Me | 1 | 5 | 100 | nd | nd |
| | | 1 | 25 | 48 | 52 | nd |
| | | 1 | 75 | 48 | 52 | nd |
| | | 2 | 5 | 100 | nd | nd |
| | | 2 | 25 | 17 | 83 | nd |
| | | 2 | 75 | 18 | 82 | nd |
| | | 10 | 75 | nd | 100 | nd |
| c | i-Pr | 1 | 5 | nd | 100 | nd |
| | | | 25 | nd | 100 | nd |
| | | | 75 | nd | 100 | nd |
| | | 2 | 5 | nd | 100 | nd |
| | | | 75 | nd | 100 | nd |

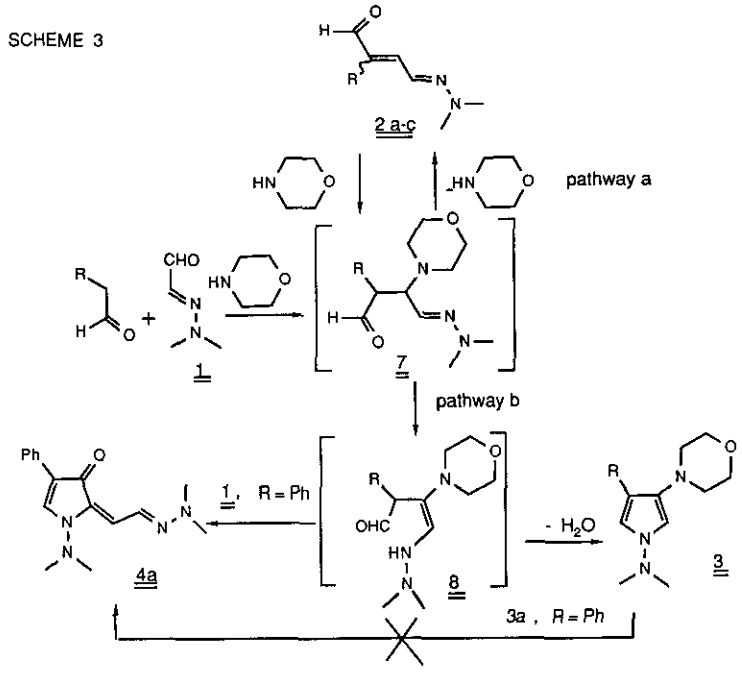
Table 1 : Aminoalkylation of enolizable aldehydes with glyoxal monohydrazone.
a) nd : not detected by nmr spectroscopy analysis.

With isovaleraldehyde, only the corresponding 3-morpholinopyrrole 3c was isolated from the reaction medium, whatever the experimental conditions were. However with propanal, the ratio between the compounds 2 and 3 is strongly dependent upon the experimental conditions. For instance at +5°C, and in the presence of the stoichiometric amount of morpholine, only the 2-methylbutene dial 2b (R=Me, R'=H) was obtained, whereas by refluxing the medium in the presence of an excess of morpholine the corresponding 3-morpholinopyrrole 3b was exclusively formed. As mentioned above, phenylacetaldehyde in the presence of 1 and different amounts of morpholine led to a mixture of pyrrolic compounds 3a and 4a. An increase of the relative amount of morpholine favors the obtention of the substituted 3-morpholinopyrrole 3a. This latter compound was obtained as the major product (80 % of the mixture), by refluxing the reaction medium with an excess of morpholine.

The mechanism of the reaction involves a first addition of morpholine on glyoxal monohydrazone 1. Thus when the latter was reacted with two equivalents of morpholine, the corresponding gem-diaminal 6 was obtained in good yields. The immonium salt of 6 was obtained by dissolving the diaminal in TFA. Moreover this salt reacted with isovaleraldehyde to yield quantitatively the 3-morpholinopyrrole 3c. Taking these results together as well as results from previous works about aminoalkylation reactions with glyoxylic

acid[2], we can assume that the first intermediate in this reaction is the Mannich base 7. This base can either lead to the unsaturated compound 2 after β-elimination (pathway a), or rearrange to the more stable enamine 8 (pathway b). When the intermediate 8 bears a formyl group, cyclocondensation can occur and lead to the corresponding 3-morpholinopyrroale 3. With phenylacetaldehyde, both enamines 3 and 8 may afford the alkylidenepyrrolin-3-one 4a by reacting with another equivalent of glyoxal monohydrazone. However the isolated pyrrole 3a did not react with 1 in the presence or absence of morpholine. This result suggests that the enamine 8 rather than the pyrrole 3 is involved in the formation of the pyrrolin-3-one 4a.

SCHEME 3




Another pathway leading to the morpholino-3-pyrrole 3 has to be considered. Thus the Knoevenagel-type reaction affording the olefin 2 may be an intermediate in this reaction. The Mannich base 7 can result from an 1,4-addition of morpholine on the Michael acceptor 2. As a support of this hypothesis, when the olefin 2a was reacted in the presence of morpholine, the pyrrole 3a was recovered quantitatively.

On the other hand, when the olefin 2a was reacted with morpholine in the presence of the glyoxal monohydrazone 1, a mixture of 3a and 4a was obtained. However with the less active olefin 2b, no reaction occurred, even by

refluxing it in the presence of morpholine. This observation is in favour of a direct transformation of the aminoalkylation product 7 into the pyrrole 3b. Taken together, these data suggest for this novel synthesis of functionalized pyrroles a multistep synthesis monitored by two equilibrium considered as key-steps. The first one is a prototropic rearrangement of the imine 7 to a more reactive enamine 8. The second one is an addition-elimination of morpholine onto the olefin 2. Both are occurring simultaneously and are strongly dependent upon concentrations of morpholine and the nature the enolic partner engaged in the reaction.

In conclusion, the aminoalkylation reaction of enolizable aldehydes with N,N-dimethyl monohydrazone of glyoxal constitutes a convenient route to obtain 1-N,N-dimethyl-3-morpholino 4-substituted pyrroles, which can be considered as new stable derivatives of unknown pyrrolin-3-ones.

## EXPERIMENTAL

Melting points were obtained on a calibrated Kofler hot-stage apparatus and are uncorrected. $^{1}H$- And $^{13}C$-nmr spectra were recorded on Bruker WP80 (80 MHz) and WP 200 Sy (200 MHz instruments), and chemical shifts are reported in parts per million ($\delta$) relative to $Me_4Si$. Ir spectra were performed on a Beckman Acculab-4 instrument. Mass spectra were recorded on a LKB 900 S apparatus.

### 4-N,N-Dimethylhydrazono-2-methyl-2-butenal 2b

To a solution of glyoxal N,N-dimethylmonohydrazone 1[5] (1.0 g, 10 mmol) in 5 ml of EtOH maintained at 4°C (ice bath) was added dropwise 1.83 ml (21 mmol) of morpholine. Then 0.85 ml (11 mmol) of freshly distilled propanal was added, and the reaction mixture was allowed to stand for two days at +4°C. The medium was extracted with $CH_2Cl_2$. The organic layer was washed with water and dried over $Na_2SO_4$. The solvent was removed in vacuo to yield 1.2 g of 2b in 85 % yield ; mp 95°C ; nmr ($CDCl_3$) $\delta$ 9.40(s, 1H), 7.05(s, 2H), 3.13(s, 6H), 2.85(s, 3H).

Anal. Calcd for $C_7H_{12}N_2O$ : C, 59.96 ; H, 8.63 ; N, 19.98. Found : C, 59.88 ; H, 8.55 ; N, 19.90.

In a similar manner was prepared 2d (R=H, R'=Ph) : yield 61 %, mp 125°C, nmr ($CDCl_3$) : $\delta$ 3.05(s, 6H), 7.00(m, 2H), 7.50(m, 4H), 8.00(m, 2H). Anal. Calcd for $C_{12}H_{14}N_2O$ : C, 71.27 ; H, 6.97 ; N, 13.85. Found : C, 71.51 ; H, 7.06 ; N, 13.70.

1-N,N-Dimethyl-3-morpholino-4-phenylpyrrole 3a

Morpholine (8.7 ml, 100 mmol) was added dropwise to a solution of glyoxal monohydrazone 1 (1.0 g, 10 mmol) in 5 ml of EtOH kept at +5°C.

*Phenylacetaldehyde (1.28 ml, 11 mmol) was added and the mixture was stirred* at room temperature for 24 h, then refluxed for another 24 h period. The mixture was extracted with $CH_2Cl_2$. The organic layer was washed with water, dried over $Na_2SO_4$ and evaporated to dryness. Chromatography of the crude solid on silica using a mixture of hexane-ethyl acetate (9:1) as eluant yielded 1.4 g of 3a (51 %) ; mp 150°C ; nmr ($CDCl_3$) : $\delta$ 7.20-7.90(m, 5H) ; 6.75(d, J=3Hz, 1H) ; 6.30(d, J=3Hz, 1H) ; 3.80(m, 4H) ; 3.35(m, 4H) ; 2.80(s, 6H).

Anal. Calcd for $C_{16}H_{21}N_3O$ : C, 70.81 ; H, 7.80 ; N, 15.48. Found : C, 70.83 ; H, 7.90 ; N, 15.57. Mass m/z (rel. intensity) 271($M^+$, 82), 227(100).

In a similar manner was prepared 3b and 3c. 3b, R=Me (10 equivalents of morpholine and a *refluxing period of 24 h) yield 60 % ; mp* 100°C ; *nmr* ($CDCl_3$) : $\delta$ 6.55(d, 1H, J=3Hz), 5.80(d, 1H, J=3Hz), 3.75(m, 4H), 3.10(m, 4H), 2.80(s, 6H), 2.00(s, 3H).

Anal. Calcd for $C_{11}H_{19}N_3O$ : C, 63.12 ; H, 9.15 ; N, 20.07. Found : C, 63.15 ; H, 9.16 ; N, 20.13. Mass m/z (rel. intensity) : 209 ($M^+$, 35), 150(21), 165(100).

3c, R=i-Pr (2 equivalents of morpholine, 48 h at room temperature), yield 70 %, mp 95°C, nmr ($CDCl_3$) $\delta$ 6.50(m, 2H), 3.80(m, 4H), 2.80(m, 5H), 2.82(s, 6H), 1.20(d, J=6Hz, 6H).

Anal. Calcd for $C_{13}H_{23}N_3O$ : C, 65.78 ; H, 9.76 ; N, 17.70. Found : C, 65.60 ; H, 9.88 ; N, 17.85.

1-N,N-Dimethyl-2-(N,N-dimethylhydrazonomethyliden)-4-phenylpyrrolin-3-one 4a

Morpholine (0.88 ml, 10.1 mmol) was added dropwise to a solution of 1 (3.0 g, 30 mmol) in 5 ml of EtOH at +5°C. After the addition of phenylacetaldehyde (1.28 ml, 11 mmol), the mixture was stirred for 24 h at room temperature, extracted with $CH_2Cl_2$, recovered and chromatographed as described above to yield 2.4 g (84 %) of 4a, mp 170°C ; nmr ($CDCl_3$) : δ 7.96(m, 2H), 7.36(m, 4H), 7.26(s, 1H), 6.68(d, 1H, J=10Hz), 3.06(s, 6H), 2.96(s, 6H). Mass m/z (rel. intensity) : 284($M^+$, 100), 240 (19), 196(26), 170(30), 44(92).

Anal. Calcd for $C_{16}H_{20}N_4O$ : C, 67.57 ; H, 7.08 ; N, 19.70. Found : C, 67.59 ; H, 7.15 ; N, 19.54.

1-N,N-Dimethyl-4-phenylpyrrolin-3-one 5a

A solution of 3a (0.271 g, 1 mmol) in 7 ml of a 6 N HCl solution was refluxed for 30 min. After cooling, the solution was neutralized with $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic layer was washed and dried over $Na_2SO_4$. Evaporation of the solvent afforded the pyrrolin-3-one 5a as an oil, which was chromatographed on silica (AcOEt/Hexane 1:1) yielding 0.12 g (60 %) of pure 5a ; nmr ($CDCl_3$) : δ 7.70(m, 2H) ; 7.13(m, 3H) ; 7.00(t, 1H, J=2Hz) ; 4.10(d, 2H, J=2Hz), 2.80(s, 6H). Ir 1665 $cm^{-1}$ (C=O).

In a same manner was prepared 5b. nmr ($CDCl_3$) : δ 6.80(m, 1H), 4.00(m, 2H), 2.80(s, 6H), 1.70(m, 3H).

2,2-Dimorpholinoethanal N,N-dimethylhydrazone 6

Morpholine (1.82 ml, 21 mmol) was added slowly at +5°C to a solution of 1 (1.0 g, 10 mmol) in 5 ml of EtOH. The mixture was kept overnight in the refrigerator. The solvent was removed in vacuo. The crude residue was triturated with cold isopropanol and filtered. The white solid (1.9 g, 74 %) was dried under vacuum. mp 97°C ; nmr ($CDCl_3$) : δ 6.50(d, 1H, J=3.6 Hz), 3.70(m, 8H), 3.20(d, 1H, J=3.6 Hz), 2.85(s, 6H), 2.55(m, 8H).

Anal. Calcd for $C_{12}H_{24}N_4O_2$ : C, 56.22 ; H, 9.34 ; N, 21.85. Found : C, 56,15 ; H, 9.40 ; N, 21.96.

Immonium salt of 6

The gem-diaminal 6 (2.5 g, 10 mmol) was dissolved in 25 ml of anhydrous THF. To the cold solution was added dropwise 3.35 g (29.4 mmol) of TFA. After removing of the solvents, the recovered oil was used without any purification for further preparations. Nmr of 6 in TFA : $\delta$ 7.50(AB, $J_{AB}$ = 9, $\Delta\delta$ = 0.95, 2H), 3.55(m, 8H), 4.20(m, 8H).

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REFERENCES

1. J.J. Bourguignon, A. Schoenfelder, M. Schmitt, C.G. Wermuth, V. Hechler, B. Charlier, and M. Maitre, J. Med. Chem., 1988, 31, 893.
2. J.J. Bourguignon and C.G. Wermuth, J. Org. Chem., 1981, 46, 4889, J. Schreiber, C.G. Wermuth, and A. Meyer, Bull. Soc. Chim. Fr., 1973, 625.
3. H.D. Perlmutter and R.B. Trattner, J. Org. Chem., 1978, 43, 2056.
4. F.H. Sangsari, F. Chastrette, and M. Chastrette, Synth. Commun., 1988, 18, 1343.
5. Th. Severin and H. Poehlmann, Chem. Ber., 1977, 110, 491 ; 1978, 111, 1564.

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