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5-Hydroxy-2*H*-pyrrol-2-ones and not 2-aminofurans are the cycloaddition products between alkyl isocyanides and benzyliden-1,3-diketones

Monica Quai,* Sara Frattini, Ugo Vendrame, Maurizio Mondoni, Simona Dossena and Enzo Cereda

Boehringer Ingelheim Italy, Chemistry Research Centre, Via Lorenzini 8, 20139 Milan, Italy

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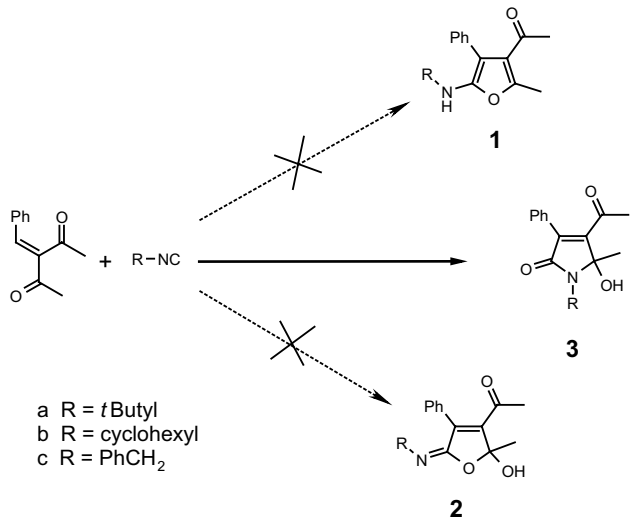
Abstract—New insights into the cycloaddition reaction between alkyl isocyanides and benzyliden-1,3-diketones are reported. 5-Hydroxy-*N*-substituted-2*H*-pyrrol-2-ones and not substituted furans, as previously reported, are formed. The proof of the structure relies on a thorough analytical investigation and X-ray crystallography.

A few years ago it was reported,[1] that the reaction between alkyl isocyanides and 3-benzylidene-2,4-pentanedione was a convenient route to prepare densely functionalized furans.

At that time, being interested in the preparation of furan derivatives, we were attracted by this new reaction, which would have made available in a clean, fast and straightforward way furans with an amino function in position 2. Indeed 2-aminofurans are quite rare[2] and, according to the previous literature, rather difficult to prepare.

The cycloaddition reaction of cyclohexyl isocyanide with 3-benzylidene-2,4-pentanedione was repeated to yield the claimed compound: 2-(*N*-cyclohexylamino)-3-phenyl-4-acetyl-5-methylfuran (Scheme 1, compound **1b**). Although the basic analytical data were similar to those reported,[3] the compound we obtained was something totally different and unexpected.

The first evidence came from HPLC-APCI/MS: the observed m/z was 314, corresponding to a protonated molecule, that is, 16 mass units higher than expected.



Scheme 1.

The molecular weight was also confirmed under different conditions (EI-MS, 70 eV).[4] In a preliminary ^{1}H NMR experiment during the acquisition of the spectra in $CDCl_3$, the appearance of a signal due to vinylic protons was observed after 20 h, suggesting the loss of a molecule of water from a hydroxy group in position α to a methyl residue. Due to this substitution pattern the presence of a chiral centre is indicated and it was confirmed by both chiral HPLC and NMR spectroscopy[5]

Keywords: Cycloaddition; Isocyanides; Diketones; Furans; Pyrrol-2-ones.

* Corresponding author. Tel.: +39-02-5355254; fax: +39-02-5355457; e-mail: mquai@mil.boehringer-ingelheim.com

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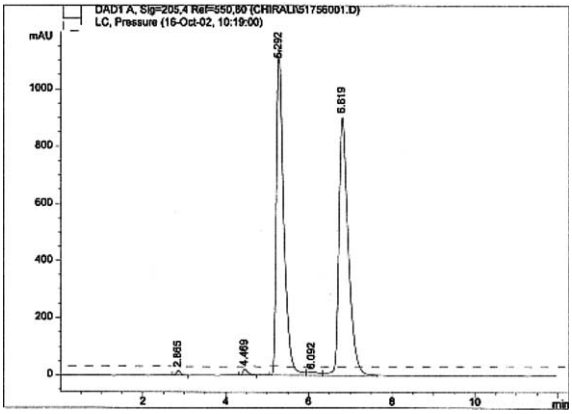


Figure 1. Chiral HPLC of compound **2b**.

on compound **2b**. A typical HPLC of the compound **2b** using a Chiralcel OD column is shown in Figure 1.

According to the analytical evidence, the structure **2b**, that is, 2-cyclohexylimino-3-phenyl-4-acetyl-5-hydroxy-5-methyl-1,5-dihydrofuran (**2b**) was initially put forward. Additional analytical data including ^{13}C NMR and IR spectroscopy and elemental analysis were in full agreement with the suggested structure.

Despite the broad set of analytical data and the previous literature reports[6] accounting for the exocyclic imine functionality, doubts still existed based on the rather unusual structure, which embraces both an imine and a hemiacetal function. These groups are normally endowed with some instability whereas the compound in our hands was stable under several different reaction conditions.[7]

To clarify the issue, an X-ray crystallographic study was undertaken on compound **2c**, which was the only one that formed suitable crystals, following recrystallization from ethanol–water.[8] At this point along with structure **1c** structure **2c** was also disproved and structure **3c** (1-benzyl-3-phenyl-4-acetyl-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one) was definitely assigned (Fig. 2).

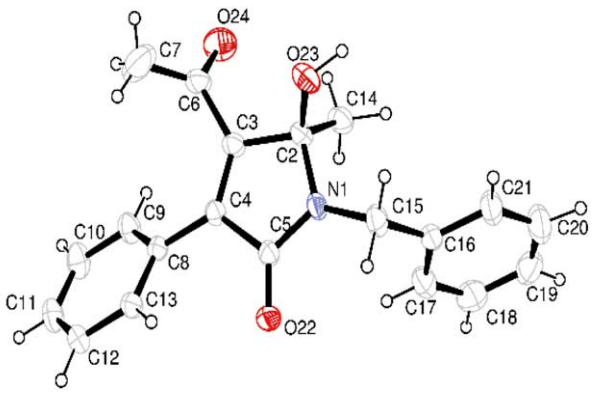


Figure 2. X-ray structure of **3c**, 1-benzyl-3-phenyl-4-acetyl-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one.

The investigation of the scope and limitation of this reaction was extended to other isocyanides (Scheme 1, R = *tert*-butyl, benzyl) such as those reported in previous literature.[1] Several attempts even under modified conditions (solvents, reaction times, temperature and anhydrous media) were carried out; nevertheless in our hands 5-hydroxy-2*H*-pyrrol-2-ones and not 2-aminofurans were the compounds isolated. On the basis of the better defined conditions, the optimized method for the reaction was established.[9]

The formation of the pyrrolone structure certainly involves a complex multistep sequence of events. To give a rational explanation a mechanism is tentatively proposed (Scheme 2).

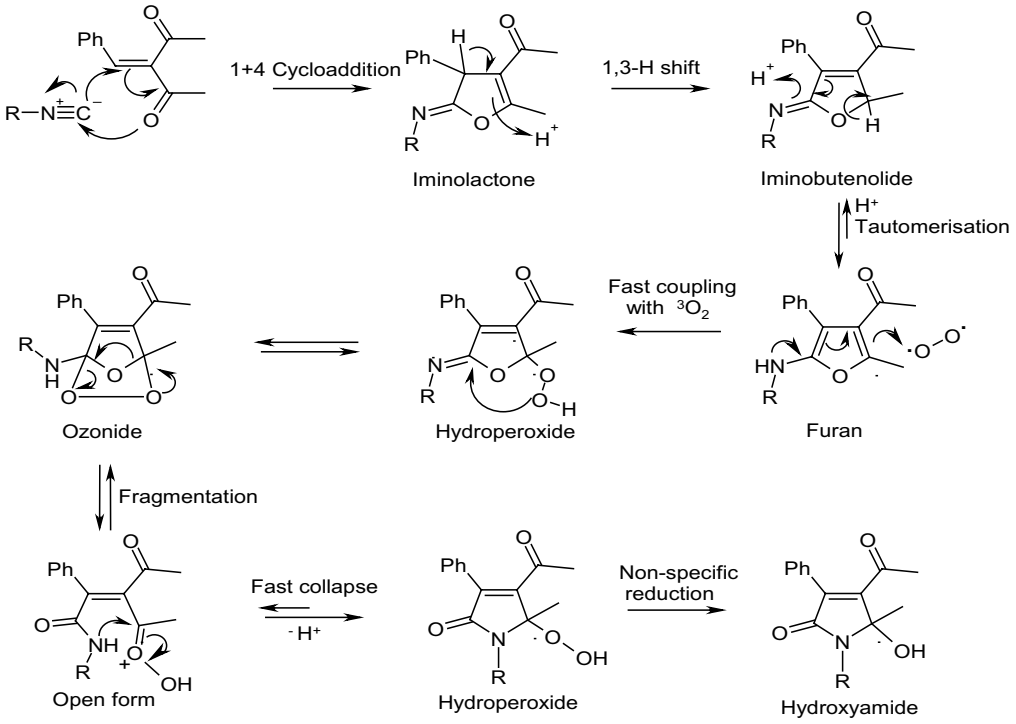
The reaction starts with the attack of the isocyanide carbon both on the carbonyl oxygen and the benzylidene carbon ([1+4] cycloaddition) yielding an iminolactone intermediate. A 1,3 proton shift leads to an iminobutenolide, which in turn is converted by tautomerization into a 2-aminofuran.

Thus in the cycloaddition reaction between benzylidene-2,4-pentanedione and isocyanides, 2-aminofurans are indeed produced but these are just intermediates, which cannot be isolated. The 2-aminofurans are quite unstable being good substrates for fast oxidation[10] by triplet oxygen at C-5. The initial hydroperoxide, following attack at C-2, is in equilibrium with an ozonide, which in turn fragments into a more stable or favored open form. Double fragmentation occurs on both the bridged five-membered rings giving rise to the carboxyamido function, the precursor of the final lactam. The open form collapses rapidly into a cyclic hydroperoxide from which the stable and isolated product is finally formed following a disproportionation reaction (Scheme 2).

A similar mechanism has been proposed in an even more complex environment.[11] The difference relies on the reaction from which the cascade flows: in that case the iminobutenolide is generated from a hydroxynitrile upon disconnection of the appropriate carbon–oxygen bond whereas in the present case through a [1+4]-cycloaddition reaction, via an iminolactone system. Moreover it is worthwhile noting that fast oxidation at C-5 occurs even when a methyl substituent is present.

To evaluate the reactivity of the functional groups of this structure, acylation of the hydroxy residue and reduction of the carbonyl group were attempted under different conditions, always with negative results. This is probably due to the existence of a relatively strong hydrogen bond between the carbonyl and hydroxy groups, leading to a pseudo-six-membered ring. Only a Grignard alkylation of the carbonyl group with methyl magnesium bromide occurred.[12]

The 5-hydroxy-pyrrol-2-one scaffold is already known and compounds based on it have been prepared,[13] but for the first time it has been obtained through a [1+4]-dipolar cycloaddition between isocyanides and alkylidene diketones.



Scheme 2. Tentative mechanism.

This new method complements those already existing and it is particularly suited to prepare advantageously in a straightforward single step, N-substituted 5-hydroxy-pyrrol-2-ones.

Acknowledgements

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References and notes

1. Yavari, I.; Shaabani, A.; Maghsoodlou, M. T. *Monatsh. Chem.* **1997**, *128*, 697.
2. (a) John, I. G.; Radom, L. *J. Am. Chem. Soc.* **1978**, *100*, 3981; (b) Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Heterocycl. Chem.* **1993**, *30*, 113.
3. Mp 145 °C versus 144–146 °C (lit.); Elemental analysis found: C, 70.30; H, 7.49; N, 4.31 versus C, 76.10; H, 7.40; N, 4.40 (lit.).
4. MS (EI); *m*/*z* (relative abundance); 313 ($M^{+\cdot}$) (17), 298 ($M-CH_3^{\cdot}$) (67), 295 ($M-H_2O^{\cdot}$) (26), 270 ($M-COCH_3^{\cdot}$) (100), 216 (62), 215 (88), 214 (67), 188 (34), 145 (89), 98 (80).
5. Chirality determinated by ^{1}H NMR using the chiral shift reagent Eu(hfc)$_3$ (Aldrich N. 16474-7).
6. Ito, K.; Kato, H.; Saegusa, T. *J. Org. Chem.* **1982**, *47*, 743.
7. The compound was unchanged after 24 h in 10% HCl aqueous solution at room temperature, 10% NH_4OH at room temperature and 8 h reflux in a solution of HCl–methanol or NH_4OH–methanol.
8. Crystallographic data (excluding structure factors) for compound **2c**, has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 220054. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
9. General procedure for the preparation of compounds **3a**, **3b**, **3c**. A solution of alkyl isocyanide (**a**, **b**, **c**, 2 mmol) in toluene (3 mL) was added to a stirred solution of 3-benzylidene-2,4-pentanedione (376 mg, 2 mmol) in toluene (15 mL). The reaction mixture was refluxed for 4 h and then evaporated to dryness. The products were purified by flash chromatography on silica gel using a mixture of dichloromethane/methanol 9:1 or by direct recrystallization from the suitable solvent. **3a**: off-white solid, 59% yield (after crystallization), mp 103 °C (from cyclohexane), TLC single spot (dichloromethane/methanol 98:2), elemental analysis calcd for $C_{17}H_{21}NO_3$ (287.36): C, 71.06; H, 7.37; N, 4.87. Found: C, 70.96; H, 7.42; N, 4.82. ^{1}H NMR (200 MHz, $CHCl_3$) δ 7.5–7.3 (m, 5H), 3.9 (s, 1H), 2.1 (s, 3H), 1.9 (s, 3H), 1.6 (s, 9H); EI-MS *m*/*z* 287 ($M^{+\cdot}$). **3b**: off-white solid, 41% yield (after crystallization), mp 145 °C (from diethyl ether), TLC single spot (dichloromethane/methanol 98:2), elemental analysis calcd for $C_{19}H_{23}NO_3$ (313.39): C, 72.82; H, 7.40; N, 4.47. Found: C, 71.93; H, 7.46; N, 4.39. ^{1}H NMR (200 MHz, $CHCl_3$) δ 7.5–7.3 (m, 5H), 3.6 (br, 1H), 3.4 (m, 1H), 2.3 (m, 2H), 2.1 (s, 3H), 1.9–1.6 (m, 5H), 1.7 (s, 3H), 1.4–1.1 (m, 3H); EI-MS *m*/*z* 313 ($M^{+\cdot}$). **3c**: colourless solid, 52% yield (after crystallization), mp 128 °C (from cyclohexane/ethyl acetate 1:1), TLC single spot (dichloromethane/methanol 98:2), elemental analysis calcd for $C_{20}H_{19}NO_3$ (321.37):

C, 74.75; H, 5.96; N, 4.36. Found: C, 74.81; H, 5.98; N, 4.36. ^{1}H NMR (200 MHz, $CHCl_3$) δ 7.5–7.2 (m, 10H), 4.8 (d, $J = 15.2$ Hz, 1H), 4.55 (d, $J = 15.2$ Hz, 1H), 3.5 (s, 1H), 2.1 (s, 3H), 1.6 (s, 3H); EI-MS m/z 321 ($M^{+\cdot}$).

10. (a) Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233; (b) Ito, K.; Yakushijin, K. *Heterocycles* **1978**, *9*, 1603.
11. Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Fong, K. C.; Choi, H. S. *J. Am. Chem. Soc.* **2002**, *124*, 2190.
12. Frattini S.; Dossena S. Unpublished results.
13. (a) Ciller, J. A.; Seoane, C.; Soto, J. L. *Ann. Chem.* **1985**, *1*, 51; (b) Procopiou, P. A.; Highcock, R. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, *3*, 245; (c) Beck, J. J.; Stermitz, F. R. *J. Nat. Prod.* **1995**, *58*, 1047.