An unusual thionyl chloride-promoted C–C bond formation to obtain 4,4’-bipyrazolones

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Abstract
Dialkyl 5,5’-dioxo-4,4’-bipyrazole-4,4’-dicarboxylates are readily obtained by the reaction of 5-hydroxy pyrazole-4-carboxylates in refluxing thionyl chloride. The obtained diesters can be transformed into the corresponding 4,4’-bipyrazoles via alkaline hydrolysis and subsequent decarboxylation. Detailed NMR spectroscopic investigations (¹H, ¹³C, ¹⁵N) were undertaken with all products prepared. Moreover, the structure of a representative 5,5’-dioxo-4,4’-bipyrazole-4,4’-dicarboxylate was confirmed by X-ray crystal structure analysis.

Introduction
Many biologically active substances, therein several drug molecules, agrochemicals, dyestuffs, compounds for optoelectronic purposes, complexing ligands and more contain a pyrazole nucleus [1-8]. Condensed pyrazoles are of special interest, as a commonly used example the phosphodiesterase 5 (PDE5) inhibitor sildenafil (Viagra®) can be mentioned [1]. In a series of former publications we described the synthesis of condensed pyrazole systems using various 4,5-disubstituted pyrazole derivatives as precursors for the annellation reaction [9-16]. Amongst these precursors 5-chloropyrazoles carrying C-substituents at the pyrazole C4 position, like 5-chloropyrazole-4-carbaldehydes or 4-esters, turned out to be particularly useful due to the easy conversion of the chloro substituent into other functional groups or its nature as a good leaving group in ring-closure reactions. In this respect we were interested in a convenient access to 1-substituted or 1,3-disubstituted 5-chloropyrazole-4-carboxylates required as valuable precursors for further functionalizations. Such compounds have been mainly prepared from the corresponding 5-aminopyrazole-4-carboxylates via (non-aqueous) diazotation and subsequent reaction with...
appropriate chlorine sources [17,18]. Additionally, some years ago we have presented a synthetic approach upon Vilsmeier reaction of 1-phenylpyrazolones with DMF/excessive POCl₃ to afford 5-chloropyrazole-4-carbaldehydes, which were oxidized to the corresponding acids (KMnO₄) and subsequently converted into the ethyl esters by treatment with EtOH/H₂SO₄ [15]. However, as the latter approach is tedious and the former one uses toxic substances we envisaged to convert the easily available 5-hydroxypyrazole-4-carboxylates 1 into the corresponding 5-chloro derivatives 2 by the action of an appropriate chlorinating agent such as POCl₃ or SOCl₂ (Scheme 1). Such conversions of a hydroxy (oxo) into a chloro function is very common with many N-heterocyclic systems, such as, for instance the transformations of 2-pyridones into 2-chloropyridines or 3-pyridazinones into 3-chloropyridazines [19,20]. In the course of the preparation of substituted 6H-pyrazolo[4,3-d][1,2]oxazoles we thus obtained the required 4-benzoyl-5-chloropyrazoles by treatment of the relevant 4-benzoyl-5-hydroxypyrazoles with POCl₃ [21].

Results and Discussion
Chemistry
However, the attempted reaction of ester 1a (R¹ = Ph, R² = H, R = Et) with POCl₃ left the starting material untouched, similarly by treatment of 1a with oxalyl chloride no conversion occurred (Scheme 2). In contrast, treatment of 1a with excessive thionyl chloride at reflux temperature resulted in a defined reaction product which, however, could not be the desired 5-chloro derivative 2a according to – amongst others – a much too large chemical shift of pyrazole C5 (δ 165.6 ppm) compared to the expected one (δ 131.3 ppm) [15]. Moreover, the OCH₂ protons revealed to be of diastereotopic character which hints to the presence of a chiral center in the molecule (Figure 1), while the molecular weight obtained by HRMS measurement ([M + Na]⁺ 485.1432) testified about the possible formation of a dimeric structure.

Lastly, by X-ray crystal structure analysis the obtained product could be determined as the dimeric structure 3a (Scheme 2, Figure 2). In addition, HRMS and elemental analysis confirmed the molecular formula. The non-equivalence of the OCH₂ protons of the ester functions can be smoothly explained by the presence of an asymmetric carbon atom at pyrazole C4/C4’. As the NMR spectra displayed a single set of signals, regarding the stereochemistry a racemic mixture or the meso-form came into consideration.

The single crystal X-ray analysis disclosed that the molecule of the newly obtained compound 3a consists of two pyrazolone residues, which are directly connected to each other by a single covalent carbon–carbon bond between the asymmetric sp³-hybridized C4 and C4’ carbon atoms to form a species with relative (4R*,4’R*)-configuration (Figure 2). The bond length of the single C4–C4’ bond is 1.544(3) Å, while the dihedral angle C5–C4–C4’–C5’ is 47.94°. The packaging of the chiral molecules (4R*,4’R*)-3a and (4S*,4’S*)-3a into a racemic crystal occurs in such a way that mirror enantiomers are interconnected to
Scheme 3: Synthesis of compounds 3a–i.

| 3 R¹ | R² | R   | Yield |
|------|----|-----|-------|
| a Ph | H  | Et  | 74%   |
| b Ph | H  | Me  | 89%   |
| c 4-Br-C₆H₄ | H | Et | 72%   |
| d 3,4-Cl₂-C₆H₃ | H | Et | 62%   |
| e Me | H  | Et  | 66%   |
| f t-Bu | H | Et | 63%   |
| g PhCH₂ | H | Et | 84%   |
| h Ph | Me | Et | 73%   |
| i Ph | Ph | Et | 75%   |

In the following, related 5-hydroxypyrazol-4-carboxylates 1b–i were subjected to the same reaction conditions (refluxing SOCl₂) and in all cases the corresponding dimers of type 3 were obtained in moderate to good yields (Scheme 3).

In order to check if these dimerization reactions also occur with other 5-hydroxypyrazoles carrying a C=O function at pyrazole C4 we subjected ketone 4 and hydrazide 5 to the same reaction conditions. In both cases, a plethora of unidentified products resulted (Scheme 4). In contrast, with aldehyde 6 a reaction...
product could be isolated in moderate yield, which can be assigned to structure 7 considering NMR data and mass spectra (Scheme 4).

The dehydrogenative homocoupling of 2-pyrazolin-5-ones (or pyrazolidin-5-ones) is well documented in the literature and proceeds under different reaction conditions such as, for instance, by air oxidation [22], under O₂ atmosphere using an O₂ balloon [23], by organic peroxides [24], phenoxy radicals [25], by treatment with phenylhydrazine at high temperatures [26,27], by nitration and subsequent heating [28], by heating with an aqueous NaHSO₃ solution [29], and by photochemistry [30,31]. In nearly all cases these reactions have been carried out with 2-pyrazolin-5-ones unsubstituted at pyrazole C₄ position or with derivatives carrying an alkyl or aryl substituent at the latter carbon atom. In contrast, only very few examples are described for pyrazolones with a C=O substructure attached to pyrazole C₄. Thus, 3-methyl-1-phenyl-4-toluoyl-5-pyrazolone (= (5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)(4-methyl-phenyl)methanone) upon treatment with oxovanadium(V) compounds afforded the corresponding 2,2',4,4'-tetrahydro-3H,3'H-4,4'-bipyrazole-3,3'-dione, whereas it was shown by EPR spectroscopy and by cyclic voltammetry that the reaction obviously proceeds via a radical mechanism [32]. To the best of our knowledge, the only such dimeric species with ester functions at pyrazole C₄, namely diethyl 1,1'-dimethyl-5,5'-dioxo-1,1',5,5'-tetrahydro-4H,4'H-4,4'-bipyrazole-4,4'-dicarboxylate (structure 3 with R¹ = Me, R² = H, R = Et) has been obtained – amongst other reaction products – by UV–vis irradiation of 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone (emorfazone) in acetonitrile [31].

Moreover, we investigated the reaction of 1a with SO₂Cl₂. Here, two reaction products – 8 and 9 – were isolated, whereas in both cases chlorination not only at the pyrazole C₄ but also in the 4-position of the phenyl ring took place (Scheme 5).

The reaction mechanism for the transformation 1 → 3 is unclear. Dimerization by air oxidation can be ruled out as performing the reaction under N₂ atmosphere provided the same result. It should be mentioned that for the oxovanadium(V)-mediated dimerization of 4-aroyl-5-hydroxypyrazoles mentioned above a radical mechanism was postulated [32]. However, in Scheme 6 we propose a hypothetical mechanism comprising a redox cyclization of an intermediate di(pyrazolyl) sulfite under elimination of sulfur monoxide.

Finally, it was shown by means of some selected examples, that compounds of type 3 can be converted into the corresponding bipyrazoles 10 upon alkaline hydrolysis and subsequent decarboxylation (Scheme 7). According to the NMR spectra,
compounds 10 are obviously present as 5-hydroxypyrazoles due to the absence of a proton attached to pyrazole C4.

**NMR spectroscopic investigation**

In Supporting Information File 1 the NMR spectroscopic data of all compounds treated within this study are indicated. Full and unambiguous assignment of $^1$H, $^{13}$C and nearly all $^{15}$N NMR resonances was achieved by combining standard NMR techniques [33], such as fully $^1$H-coupled $^{13}$C NMR spectra, APT, gs-HSQC, gs-HMBC, gs-HSQC-TOCSY, COSY, TOCSY and NOESY spectroscopy. Figure 4 shows the thus assigned $^1$H, $^{13}$C and $^{15}$N NMR chemical shifts for model compound 3a.

![Figure 4: $^1$H NMR (italics), $^{13}$C NMR (normal letters) and $^{15}$N NMR (in bold) chemical shifts of 3a (in CDCl$_3$).](https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-110-S1.pdf)

**Conclusion**

The reaction of 5-hydroxypyrazole-4-carboxylates 1 with thionyl chloride does not lead to the corresponding 5-chloropyrazole congeners but induces dimerization to afford the relevant diazyl 5,5'-dioxo-4,4'-bipyrazole-4,4'-dicarboxylates of type 3.

**Supporting Information**

Supporting Information File 1

Experimental details and compound characterization. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-110-S1.pdf](https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-14-110-S1.pdf)

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