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Site- and Stereoselective Synthesis of Bridgehead Tetrahydropyrrolo[2,3-*c*]pyridines From Ketoximes and Acetylene Gas in Two Synthetic Operations

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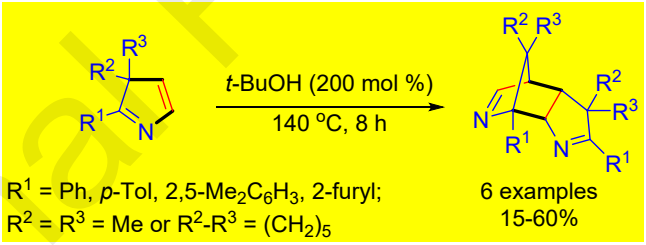
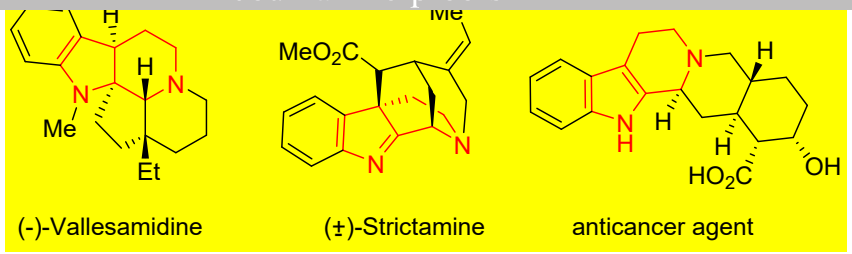
Abstract: 3*H*-Pyrroles, synthesized in one-pot from ketoximes and acetylene gas in a KOH/DMSO system, undergo [4+2] cyclodimerization in the presence of *t*-BuOH (closed vessel, autogenic pressure, 140 °C, 8 h) to site- and stereoselectively afford partially hydrogenated bridgehead pyrrolo[2,3-*c*]pyridines in 15-60% yield. An essential feature of this synthesis is the activating effect of *t*-BuOH which is attributed to reversible H-bonding of the 3*H*-pyrroles.



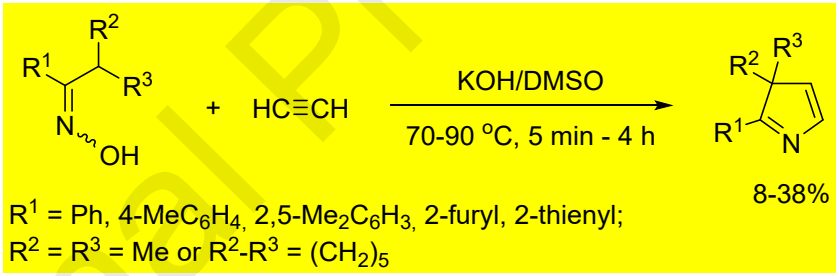
Keywords: acetylene, 3*H*-pyrrole, pyrrolopyridine, H-bonding, Diels-Alder dimerization

The fused pyrrolopyridine core, formed from pyrroles and pyridines, represents an important synthetic platform for medicinal chemistry. This core is found in various natural products (e.g. vallesamidine, phalarine, strictamine) and as a structural motif in antibacterial and anticancer agents [1], inhibitors of matrix metalloproteinase [2], orexin receptor antagonists [3], and therapeutics for the treatment of central nervous system disorders [4] (Scheme 1). Therefore, the development of expedient approaches to this bicyclic scaffold is an urgent synthetic task [5].



Scheme 1. Representative examples of fused pyrrolopyridines

Looking for such approaches we have analyzed a number of possible reaction sequences, which could provide a short atom-, step- and reactor-economic access (in context of the PASE paradigm [6]) towards functionalized pyrrolopyridines. A clue to the solving this problem might be the recent report on the alkaloid longeracemine [7], which demonstrated a potential application of 3*H*-pyrroles as a springboard to construct complex molecular architectures. Indeed, these compounds can be used as 1,3-diene components in [4+2] cycloadditions. This assumption happens to be in line with our current interest in 3*H*-pyrrole chemistry. These nonaromatic, energy rich pyrrole isomers were synthesized by us in a one-pot procedure from ketoximes and acetylene gas in a KOH/DMSO system (Scheme 2) [8].

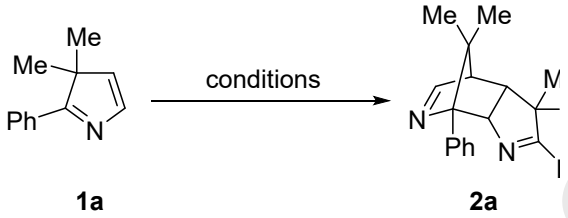


Scheme 2. Synthesis of 3*H*-pyrroles from ketoximes and acetylene gas in the KOH/DMSO system.

It seemed probable that this reaction could initiate a two-step construction of pyrrolopyridines, provided the appropriate conditions for their auto [4+2] cycloaddition could be developed. A hope for the success of such a synthetic scheme followed from our previous observation that certain 3*H*-pyrroles upon long-term storage (9.5 months) were transformed into the diverse tetrahydropyrrolopyridine structure [9]. Such a short-cut to the above partially hydrated heterocyclic systems meets the interests of modern medicinal chemistry which today focuses on the study of semi-aromatic molecules. This trend is now gaining strength [10] because sp^3 carbon centers render the molecules potentially chiral, 3D-structured, and more soluble which improves the odds for drug discovery.

In this communication, we describe our efforts to substantiate this two-step approach towards pyrrolopyridines. Below it is shown that our initial assumptions were accurate. However, our first attempts to realize this auto-Diels-Alder condensation failed, as illustrated by the experiments at dimerising 2-phenyl-3,3-dimethyl-3*H*-pyrrole **1a** (Table 1).

Table 1. Attempted cyclodimerization of 2-phenyl-3,3-dimethyl-3*H*-pyrrole **1a** to 3,3,8,8-tetramethyl-2,7-diphenyl-3a,4,7,7a-tetrahydro-3*H*-4,7-methanopyrrolo[2,3-*c*]pyridine **2a**.



1a **2a**

Entry	T (°C)	t (h)	Ratio of **1a**:**2a**[a]
1	100	6	95:5
2	120	6	93:7
3	140	6	86:14
4	150	6	60:40[b]
5	160	6	35:65[b]
6[c]	110	82	45:55[b]
7[d]	202	2-15	-[b]

[a] According to ^{1}H NMR spectroscopy of the crude reaction.
[b] Significant tar formation was observed.
[c] In toluene.
[d] In NMP.

Neither temperature nor time variation were effective. At 100 °C for 6 h, only trace amounts of the desired dimer **2a** were detected (Entry 1). Further increase of the reaction temperature to 160 °C facilitated the dimerization, but was accompanied by significant tar formation (Table 1, Entries 2-5). A similar extent of the dimerization of 3*H*-pyrrole **1a** together with tar formation took place, when it was heated at reflux in toluene (110 °C, 82 h), while reflux in *N*-methylpyrrolidone (202 °C, 2-15 h) gave no product **2a** (the starting pyrrole **1a** was consumed entirely) and the same strong resinification occurred.

This reluctance of 3*H*-pyrrole **1a** towards cyclodimerization is probably due to the fact that both 1,3-diene and dienophile components are of the same electron-rich nature, hence they lack the mutual electron orbital affinity. This inference is in line with publications [11] regarding the successful Diels-Alder condensation of 3*H*-pyrroles with selected electron-deficient dienophiles, including an intramolecular version of the cyclization of 3*H*-pyrroles having unsaturated alkenyl side chains at position 3, albeit under harsh conditions (245 °C, 65 h) [12]. Also, the inverse-electron-demand Diels-Alder condensation of electron-deficient pentachloro-3*H*-pyrrole with electron-rich dienophiles was successful [13]. Therefore, we employed acidic

reagents to reduce the basicity of the imine moiety, although in equilibrium both electron-deficient (H-bonded) and electron-rich (free) 3*H*-pyrroles are present. The selective results of these experiments are shown in Table 2.

Only *tert*-butanol demonstrated satisfactory activity (Entry 8), while other protogenic additives did not display any positive effect (Entries 11-14). Both trifluoroacetic acid and aluminium chloride as strong Brønsted and Lewis acids (Entries 15-17) led to decomposition of the starting 3*H*-pyrrole **1a**. Thus, the mild activating effect of *t*-BuOH has been established. After a thorough study of this process, including variation in additive loading, reaction time and temperature (Entries 2-10), the following optimised conditions for the dimerization of 3*H*-pyrrole **1a** were found: *t*-BuOH (200 mol%), heating (closed vessel, autogenic pressure of *ca*. 3-3.5 atm [14]) at 140 °C, 8 h (Table 2, Entry 8), which provided the desired dimer **2a** in 60% isolated yield.

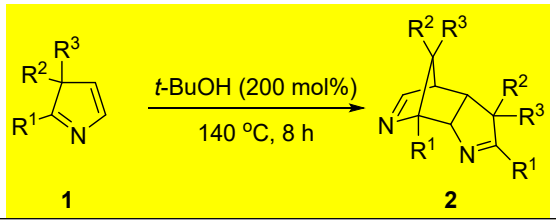
Table 2. Effect of additives on the dimerization of 3*H*-pyrrole **1a**.

Entry	Additive (mol%)	T (°C)	t (h)	Ratio of **1a**:**2a**[a]
1	*n*-BuOH (100)	100	6	13:47[b]
2	*t*-BuOH (100)	100	8	68:32
3	*t*-BuOH (200)	100	8	55:45
4	*t*-BuOH (300)	100	8	73:27
5	*t*-BuOH (200)	100	16	55:45 (46%)[c]
6	*t*-BuOH (200)	80	8	88:12
7	*t*-BuOH (200)	120	8	43:57 (51%)[c]
8	***t*-BuOH (200)**	**140**	**8**	**35:65 (60%)**[c]
9	*t*-BuOH (200)	140	4	38:62
10	*t*-BuOH (200)	140	12	38:62[d]
11	CF_3CH_2OH (100)	100	8	89:11
12	PhOH (100)	100	8	93:7
13	H_2O (100)	100	8	90:10
14	AcOH (100)	100	8	90:10
15	TFA (10)	100	8	indefinable[d]
16	$AlCl_3$ (10)	100	8	95:5
17	$AlCl_3$ (100)	100	8	indefinable[d]

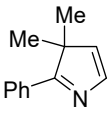
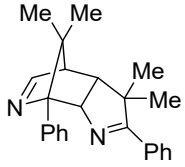
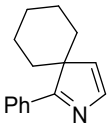
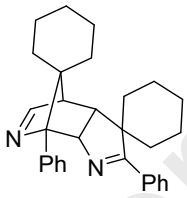
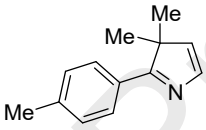
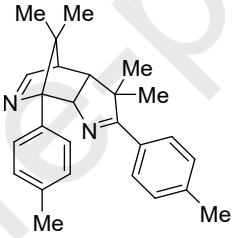
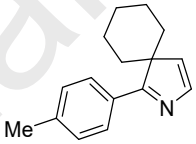
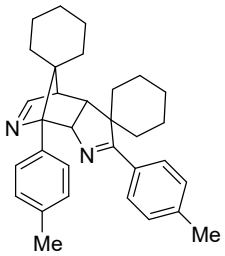
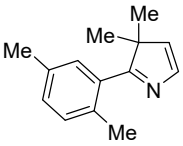
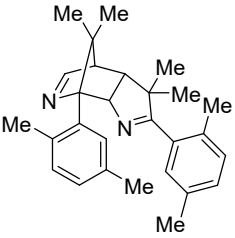
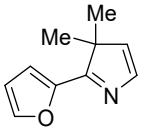
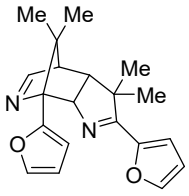
[a] According to ^{1}H NMR spectroscopy of the crude reaction.
[b] Product of nucleophilic addition (40%) was observed.
[c] Isolated yields are given in parentheses.
[d] Significant tar formation was observed.

These reaction conditions were then applied to a series of diverse 3*H*-pyrroles **1b-f** (Table 3). Although in all cases only the target dimers **2** and starting 3*H*-pyrroles **1** were observed in the reaction mixture (according to ^{1}H NMR spectroscopy), the other mode of starting material conversion was tar formation.

Table 3. Dimerization of 3*H*-pyrroles **1a-f**.



1 **2**

Entry	3*H*-Pyrrole **1**	Cyclodimer **2**	Yield (%)
1	 **1a**	 **2a**	60
2	 **1b**	 **2b**	51
3	 **1c**	 **2c**	49
4	 **1d**	 **2d**	49
5	 **1e**	 **2e**	–[a]
6	 **1f**	 **2f**	22

[a] According to ^{1}H NMR spectroscopy of the crude reaction both with and without *t*-BuOH, the ratio of **1e**:**2e** was *ca*. 85:15.

In the cyclodimerization studied, the asymmetry of the dienes and dienophiles might result in the formation of a number of site- and stereoisomeric dimers. Pleasingly, the transformation of 3*H*-pyrroles **1** to dimers **2** turned out to be a regio- and *endo*-diastereoselective process that was unambiguously proved by the X-ray diffraction of dimer **2a** (Fig. 1), as well as ^{1}H, ^{13}C and ^{15}N NMR spectroscopy (2D COSY, NOESY, HMBC, HSQC techniques were also employed).

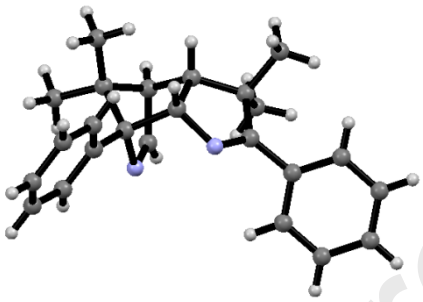


Figure 1. ORTEP diagram of dimer **2a** as determined by X-ray analysis.

The activating effect of *t*-BuOH is likely associated with reversible H-bonding between the highly basic imine nitrogen of 3*H*-pyrroles and *t*-BuOH. Consequently, in the reaction mixture both H-bonded, *i.e.* electron-deficient 3*H*-pyrroles and their non-bonded counterparts are present. The adverse influence of further increasing the *t*-BuOH content (Table 2, entry 4) possibly originated from augmentation of the H-bonded form concentration. Likewise, the higher acidity additives (Table 2, Entries 11-14) strongly diminish the concentration of the non-bonded form.

This mechanistic rationalization is in line with the substituent effect observed in the dimerization (Table 3). The lowest yield (15%) in the case of 3,3-dimethyl-2-(2,5-dimethylphenyl)-3*H*-pyrrole **1e** is predictable when accounting for the fact that nitrogen atom H-bonding is sterically restricted by the *ortho*-methyl group of the substituent. The decreased yields in cases of 2-furyl (22%, Entry 6) and *p*-tolyl-3*H*-pyrroles (49%, Entries 3 and 4) result from their donor nature that reduces the acceptor effect caused by H-bonding. The MO analysis of both 3*H*-pyrrole **1a** and its H-bonded by *t*-BuOH form did not show significant differences in the HOMO and LUMO energies and their localizations (see ESI for details). Nevertheless, the activating effect of *t*-BuOH, as attributed to its possible coordination with the transition state, decreases the activation energy from 16.1 to 10.9 kcal/mol for non-catalytic and *t*-BuOH-catalyzed transformations, respectively (wB97XD level for both, Fig. 2).

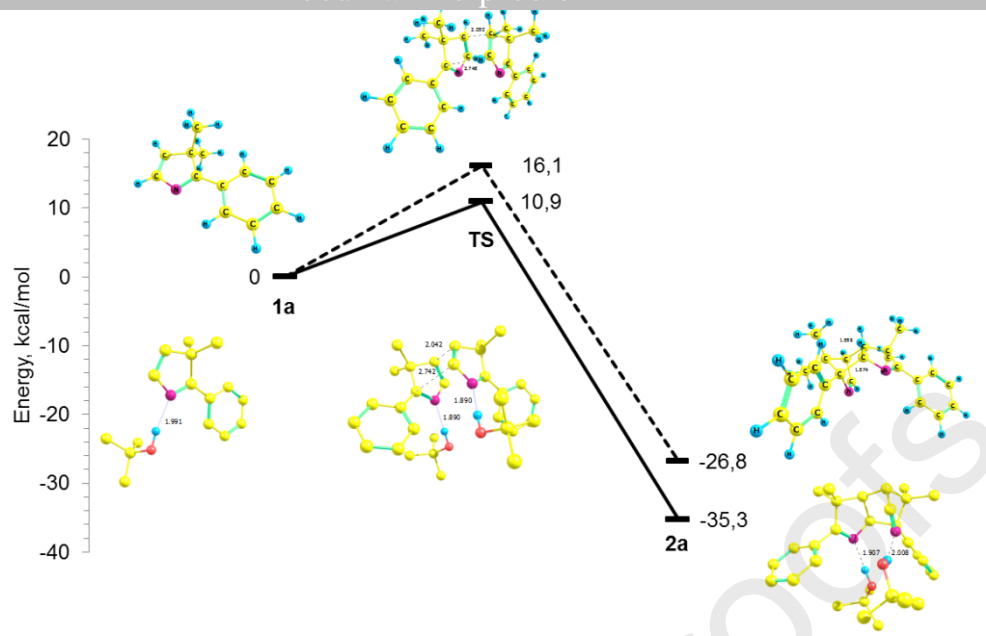


Figure 2. Energy diagram [wB97XD/6-311+G(d,p)] for non-catalytic (dashed line) and catalytic (solid line, hydrogen atoms are omitted for clarity) **1a→2a** transformation.

Another question to be answered is the electronic characterization of the studied cyclization. According to the quantum-chemical calculations, activation of the dimerization by only one molecule of *t*-BuOH is equal to 13.1 kcal/mol. Notably, the difference in energy of the two transition states in which *t*-BuOH coordinates with the diene or dienophile component is *ca*. 0.01 kcal/mol and therefore cannot be an unambiguous parameter for the electronic nature assignment. Nevertheless, since for the successful implementation of the inverse-electron-demand Diels-Alder reaction it is necessary to activate 3*H*-pyrrole as the diene component significantly (e.g. by introducing five chlorine atoms [13]) one may conclude that the described dimerization represents a formal Diels-Alder condensation between electron-rich dienes and electron-deficient dienophiles, *i.e.* a normal electron-demand case.

In conclusion, we have developed a two-reaction strategy to provide site- and stereoselective access, starting from simple and readily available materials (ketoximes, acetylene gas, KOH, DMSO, *t*-BuOH), to novel pharmaceutically prospective structures of a higher molecular complexity, 3*H*-4,7-methanopyrrolo[2,3-*c*]pyridines. The strategy comprises of the reaction of ketoximes with acetylene gas in the KOH/DMSO system to afford non-aromatic pyrrole congeners, 3*H*-pyrroles, which then undergo [4+2] cyclodimerization under the action of excess *t*-BuOH. The activating effect of the latter on this cyclodimerization is due to the reversible H-bonding of 3*H*-pyrroles leading to partially protonated species, which act as electron-deficient dienophiles relative to the remaining non-bonded electron-rich partners. The

synthesized isomerically pure bridgehead tetrahydropyrrolo[2,3-*c*]pyridines represent potentially rewarding compounds for medicinal chemistry.

Acknowledgements

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Site- and Stereoselective Synthesis of Bridgehead Tetrahydropyrrolo[2,3-*c*]pyridines From Ketoximes and Acetylene Gas in Two Synthetic Operations

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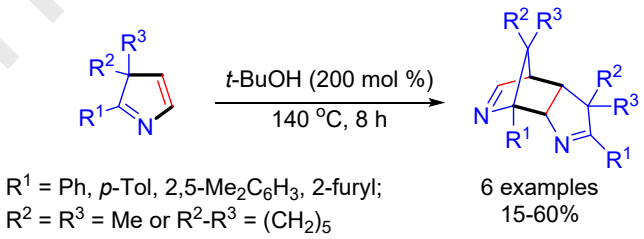

R^1 = Ph, *p*-Tol, 2,5-$Me_2C_6H_3$, 2-furyl;
R^2 = R^3 = Me or R^2-R^3 = $(CH_2)_5$

6 examples
15-60%

Highlights:

An efficient two-reaction strategy approach to tetrahydropyrrolo[2,3-*c*]pyridines.

Available starting materials are used.

The tetrahydropyrrolo[2,3-*c*]pyridines were obtained site- and stereoselectively in good yields.

The first example of organocatalytic [4 + 2]-cyclodimerization of 3*H*-pyrroles.

Structural elucidation using NMR and single crystal X-ray studies.