GREEN CHEMISTRY FOR PREPARATION OF OLIGOPYRROLE MACROCYCLES PRECURSORS: NOVEL METHODOLOGY FOR DIPYRROMETHANES AND TRIPYRROMETHANES SYNTHESIS IN WATER

Vladimír KRÁL[1,*], Petr VAŠEK[2] and Bohumil DOLENSKÝ[3]

Department of Analytical Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic; e-mail: [1] kralv@vscht.cz, [2] vasekp@vscht.cz, [3] dolenskb@vscht.cz

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Dedicated to Professor Ivan Stibor on the occasion of his 60th birthday.

A novel methodology for preparation of linear oligopyrroles is presented. Synthetic protocol uses water as a solvent for acid catalysed condensation of an aldehyde or ketone with unsubstituted pyrrole. While the most procedures for the above-mentioned compounds are performed in organic solvents, or large excess of pyrrole (used as solvent), we present here a novel, mild and efficient procedure for selective preparation of linear oligopyrroles in aqueous environment. Preparation of dipyrromethanes **3** and tripyrromethanes **4** was optimised by varying the molar ratio and concentrations of starting compounds (aldehyde to pyrrole) and acid catalyst. The high initial concentration of aldehyde and pyrrole leads to the preferential formation of **3**, where the driving force for the product formation is precipitation of **3** from water solution; the reaction proceeds at room temperature within a couple of minutes in excellent yields. On the other hand, low concentration of starting compounds led to preferential formation of tripyrromethanes **4**. Formation of **3** and **4** can also be controlled by the initial ratio of aldehyde and pyrrole, where generally the ratios over 1:6 gave mostly **3**. Application of this synthetic protocol for ketones revealed that only **3** are formed, regardless of the ratio of starting compounds, which is interpreted as a result of lower reactivity of ketones in this particular condensation reaction.

Keywords: Oligopyrrole macrocycles; Porphyrins; Calixpyrrols; Pyrrols; Dipyrromethanes; Tripyromethanes; Aldehydes; Condensation in water; Green chemistry.

Green chemistry is the term of recent years and usually means nature-friendly performance of reactions without harmful effects. The most waste is produced not from reagents but from the reaction medium, solvent. The best solvent from this point of view is obviously water, which is a solvent of choice for future chemical industry. Therefore, there is growing interest in performance of organic reactions in water not only for environmental

reasons, but also as water is a unique solvent (polarity, dielectric constant, specific H-bonding, etc.). There is, of course, one severe limitation to the use water as a medium for organic reactions, which is limited water solubility of the most organic compounds. Although, the chemistry of today knows that reactions can take place even in the solid state, the necessity of liquid medium for most organic reactions remains. It is generally accepted that everything is soluble in everything, and the question is only, how much. The low reagent concentrations results in the low reaction rates, which is the main limitations of water as reaction solvent. The concentration of reagents can be enhanced by adding of usually ionic organic compounds for formation of micelles, or dissolving organic molecules in water using, e.g., cyclodextrin inclusion complex formation, or just adding some polar organic compounds soluble in water like alcohols.

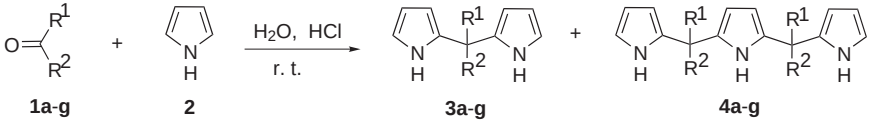
The water medium has been already successfully used e.g. for synthesis of the lowest homologs of tetraalkylmesoporphyrin[1], Michael additions[2,3], zinc metal-mediated chemoselective reduction of nitroarenes[4], reduction of aromatic rings using a Raney Ni-Al alloy[5], dechlorination of chlorobiphenyls[6], or even a Grignard-like reaction[7].

Our group is interested in chemistry of oligopyrrole macrocycles, which has developed within the last decade, going from classic porphyrin analogues to contracted and expanded porphyrinoids as well as to systems with stopped or fully removed conjugation[8]. Simple synthetic methodology was sufficient for preparation of symmetrical porphyrin derivatives, where the most popular[9] became Rothemund and Adler-Longo 4×1 approaches. By this methodology, Japanese authors recently reported preparation of conjugated higher oligopyrrole macrocycles, when pentafluorobenzaldehyde or 2,6-dichlorobenzaldehyde was used[10]. We have recently reported also a great potential of oligopyrrole macrocycles for analytical[11] as well as medicinal[12] applications and molecular recognition[13]. But now, with new development in the area of inverted (confused)[10], expanded porphyrins[8,14], there is a great need for simple and reliable synthesis of convenient building blocks for the novel oligopyrrole macrocycles. In other words, the further development in this area depends on availability of building blocks, mainly for linear oligopyrrole systems, dipyrromethanes **3** and tripyrromethanes **4**.

In spite of relative simplicity, a general, reliable and simple method for the preparation of linear oligopyrroles remains a challenge. Even simple molecules like dipyrromethanes **3** with β-unsubstituted pyrrole have been reported by Lindsey only a couple of years ago by reaction of aldehydes with excess of pyrrole. Dipyrromethanes with β-substituted pyrrole are usually prepared by multistep synthesis, based on formation 5,5′-bis esters of

dipyrromethanes[9] followed by hydrolysis and decarboxylation. For unsubstituted pyrroles, the reactivity for electrophilic substitution at β-pyrrole position, which has been ignored for quite a long time, and only recently was properly addressed. This factor was recognised and used for construction of so-called confused, or inverted porphyrins and expanded porphyrins (for review see Furuta[15]). Another problem comes from reactivity of primarily formed dipyrromethanes (they react with another aldehyde and pyrrole) leading to tripyrromethanes and even higher analogues[16]. The Lindsey approach how to avoid such undesirable effect is using a large excess of pyrrole. Such condition, where pyrrole is used as a solvent, gave almost pure dipyrromethane derivatives[17,18]. But in most so far described cases, tedious chromatographic separation of a rather complex reaction mixture is a usual scenario. There are many examples of tuning old techniques to selectively produce dipyrromethanes[18] or tripyrromethanes[16] with variety depending on nature of carbonyl compound.

This communication describes a novel approach to building blocks for synthesis of oligopyrrole macrocycles, based on preparation of dipyrromethanes **3** and tripyrromethanes **4** by the reaction of unsubstituted pyrrole with organic carbonyl compounds in water (Scheme 1).



1a-g **2** **3a-g** **4a-g**

	R^1	R^2
a	H	Ph
b	H	C_6F_5
c	H	$_4$-O_2N-C_6H_4
d	H	$_4$-CH_3O-C_6H_4
e	H	$_2$-naphthyl
f	CH_3	Ph
g	CH_3	CH_3

SCHEME 1

RESULTS AND DISCUSSION

Our idea of novel synthesis of linear oligopyrromethanes from aldehydes and pyrrole came from the known inclusion complexation of aromatic aldehydes by β-cyclodetrin (β-CD). Here, in our design, we expected efficient inclusion complex formation of β-CD with aldehyde leading to solubilisation in water, where pyrrole is partly soluble[19]. This experimental design led to homogeneous solutions in water after addition of acid catalyst (in this set of experiments we have used HCl). After stirring at room tempera-

ture, we observed within minutes to hour (depending on the reactivity of **1**) precipitation of the product from water solution, which is in our scenario expected to be dipyrromethane **3**. We understand precipitation as a result of poor complexation of a much larger product and, consequently, low inclusion complex affinity to dipyrromethane **3**. The MS and NMR analysis showed that the precipitate, which is easily filtered off, contains the desired dipyrromethane **3** together with tripyrromethane **4** and some higher oligopyrromethanes, while β-CD remains in water solution and can be reused again.

However, in a control experiment, surprisingly, we have found that β-CD is not necessary and the reaction takes place even without the β-CD presence. This finding is interpreted that reaction can proceed as heterogeneous as well. Our results revealed that even partial solubility of starting compounds is sufficient for the desired transformation.

A work describing similar finding as we are presenting here has been published recently[20]. We repeat their technique and found some inconsistency. The authors do not describe tripyrromethanes **4** as by-products of the reactions, which can be given by the fact that they performed only GC analysis of the crude product. It is known that tripyrromethanes have significantly higher retention times[21] and higher oligopyrromethanes are usually observed by LC analysis of the reaction mixture. Therefore, we have made crude product analysis by detailed studies of NMR data of representative sample of the reaction product.

Our results are summarised in Tables I–VII.

In Table I can be seen our experiments with 1 equivalent of β-CD (row a) or without β-CD (row b) comparing the result we have obtained by reproducing the described reaction procedure[20] (row c). It has to be noted that poor preparative yield is due to product adhering to flask wall and stirring

TABLE I
The condensation reaction of benzaldehyde with pyrrole in water

β-CD	Ratio **1a**[b]:**2**	Purity %	Ratio **3a**:**4a**	Yield[a] %	Conditions
+	1:5	96	63:37	49	1 h, r.t.
–	1:5	96	68:32	58	1 h, r.t.
Ref.[20]	1:5	92	50:50	47	1 h, 100 °C

[a] Calculated overall yield of **3a** and **4a**. [b] Concentration of **1a** 19.6 mmol/l.

bar. In order to get precise information on product distribution, we have used extraction for product isolation (not only filtration).

The reactions with extraction work-up demonstrate (Table II) practically no effect of any CD on the course of the reaction again. Note, that 1 equivalent of CD to benzaldehyde, concentration of benzaldehyde was 12.3 mmol/l (concentration of saturated solution of benzaldehyde in water[22] is 31.1 mmol/l), ratio **1a**:**2**, and reaction time 15 min were used. Small differences in conversion of aldehyde (reaction rate) can be found but explanation of such small differences could be only speculative.

In order to understand factors governing this condensation, we performed variation of conditions, including ratio of aldehyde (or ketone) to pyrrole, reaction time, temperature, and concentration of acid catalyst.

Then we tried several carbonyl compounds under various reaction conditions to reveal the reaction patterns. Table III shows some other aldehydes reacting under our conditions where concentration of aldehyde 11.7 mmol/l, reaction time 17 h, room temperature, and dilute hydrochloric acid (0.12 mmol/l) were used. Also the effect of the aldehyde-to-pyrrole ratio on resulting ratio of dipyrromethane **3** to tripyrromethane **4** can be easily seen.

We applied earlier HPLC with reverse phase as analytical tool for following course of reaction, but our conclusion is that ^{1}H NMR is the best analytical method for evaluation of product composition and conversion. According to expectation, a higher excess of pyrrole leads to higher selectivity, and dipyrromethane **3** is formed as major product.

Our experiments revealed that course of reaction in aqueous environment (mainly the ratio **3**:**4**) is driven by the ability of products to precipitate from water (product solubility). If the product remains in solution, sub-

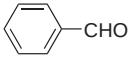
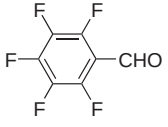
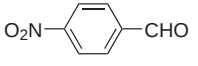
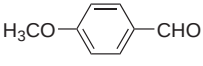
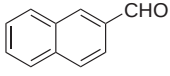
TABLE II
The effect of α-, β- and γ-cyclodextrin on the studied condensation of benzaldehyde and pyrrole

CD	Conversion %	Ratio **3a**:**4a**
α-CD	65	50:50
β-CD	55	47:53
γ-CD	58	45:55
–	49	41:59

sequent condensation of **3** takes place leading to predominant formation of product **4**. The solubilities of starting aldehyde in water vary dramatically, some aldehydes, e.g. benzaldehyde, are soluble in water and the reaction proceeds initially as homogeneous under our conditions, but product distribution is not influenced. Oppositely to benzaldehyde **1a**, nitrobenzaldehyde **1c** and naphthylaldehyde **1e** never formed a solution and the reaction proceeded under heterogeneous condition. In the case of **1c** very good selectivity and conversion was observed. The aldehyde **1e** reacted much slower (see the conversion of aldehyde) and no formation of tripyrromethane **4e** has been detected.

From our results we can draw the conclusion that the driving force of conversion is precipitation of the product. The reaction can proceed initially as homogeneous (for water-soluble aldehydes) or heterogeneous (for aldehydes and ketones slightly soluble in water).

TABLE III
The results of the reactions of pyrrole (**2**) with aldehydes (**1**)

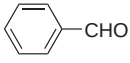
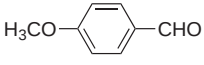
Row	Aldehyde		Ratio **1**:**2**	Ratio **3**:**4**	Purity %	Conversion %
a		**1a**	1:2	41:59	70	100
b			1:3	52:48	81	100
c			1:6	70:30	89	100
d		**1b**	1:2	75:25	92	>95
e			1:3	83:17	89	99
f			1:6	92:8	88	99
g		**1c**	1:3	85:15	91	100
h			1:6	95:5	94	100
i		**1d**	1:2	50:50	75	90
j			1:6	79:21	90	95
k		**1e**	1:2	[a]	52	48
l			1:6	[a]	60	66

[a] Tripyrromethane **4e** has not been identified in the reaction product.

Therefore, we have studied the influence of reagent concentrations on the product distribution under the same conditions. Table IV demonstrates that higher concentrations of reagents lead to good selectivity for dipyrromethane **3**. Surprisingly, significantly lower concentrations of reagents lead to the formation of tripyrromethane **4** with good selectivity. In addition, the row f shows the result of reproducing the recently published work[20] (reaction temperature 100 °C) but with extraction of all products. It is clear that our described procedure enables the product preparation under significantly milder conditions.

The main question from the synthetic point of view is whether **3** or **4** can be selectively formed. These results suggest changing the reaction conditions to obtain higher selectivity of formation of tripyrromethane **4a**. In Table V (in all cases 0.12 M HCl was used) is showen that the best results have been found when the 1:1 ratio of reagents is used, mainly because of product purity. Also see Table III (rows g and h) for 4-methoxybenzaldehyde (**1d**). Note, the row b shows the results of reaction when mixtures of aqueous HCl and methanol (1:1) have been used. Methanol enhances the solubility of reagents and products, which leads to a significantly lower purity, in other words, to higher oligomerisation degrees. The reason is that the product does not precipitate from the mixture.

TABLE IV
Influence of reagent concentrations on the condensation reaction

Row	Aldehyde	Conc. of **1** mmol/l	Ratio **1**:**2**	Ratio **3**:**4**	Purity %	Conversion %
a	 **1a**	187.9	1:2	82:18	48	99
b		47.0	1:2	64:36	65	99
c		11.7	1:2	37:63	75	99
d		2.0	1:2	15:85	63	99
e		47.0	1:5	88:12	95	93[a]
f[20]		1400	1:5	76:24	70	100
g	 **1d**	11.7	1:2	50:50	75	90
h		1.2	1:2	14:86	70	96

[a] Quenched after 15 min.

We also explored the effect of acid concentration (Table VI). All experiments were made with concentration of **1a** 11.7 mmol/l, **1a**:**2** ratio 1:2, reaction time 17 h. It is clear that too concentrated acid gives lower purity (the conversions were almost 100%).

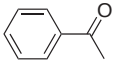
TABLE V
Optimisation of the condensation conditions for tripyrromethane **4a**

Row	Ratio **1a**:**2**	Ratio **3a**:**4a**	Purity %	Conversion %	Conc. of **1a** mmol/l
a	1:2	82:18	48	99	187.9
b	1:2	38:62	16	100	11.7
c	1:2	15:85	63	99	2.0
d	2:3	15:85	38	95	1.2
e	1:1	15:85	73	100	11.7
f	1:2	34:66	84	100	11.7

TABLE VI
Influence of HCl concentration on condensation **1a** with **2**

Ratio **3a**:**4a**	Purity %	Conc. of HCl mol/l
40:60	47	1.2
37:63	75	0.12
32:68	72	0.012

TABLE VII
Variation of carbonyl starting compounds: reactions of pyrrole with ketones

1	Ratio **1**:**2**	Ratio **3**:**4**	Purity %	Conversion %	Conc. of **1** mmol/l	Reaction time, h
 **1f**	1:2	–	79	35	11.7	17
	1:6	–	91	75	11.7	17
	1:3	–	85	>88	11.7	75
 **1g**	1:2	Mix	10 **4g**	–	5.9	17
	1:1	Mix	40 **4g**	–	11.7	17

Finally, we have employed in the reaction some ketones using diluted hydrochloric acid (1:99) (Table VII). We obtained good result for acetophenone and bad for acetone. Again we see the reason is a low solubility of acetophenone and unlimited solubility of acetone in water, although the reactivity of the ketones also plays a certain role. With acetone, very complex mixture was formed (no precipitation of product) and we have been able to estimate only the content of tripyrromethane **4g**. In addition, we found that camphor or cholestenone does not react even at higher temperature (100 °C), with or without the methanol addition to increase the solubility.

CONCLUSION

We present here a method for preparation of dipyrromethanes **3** and tripyrromethanes **4** in aqueous solution under very mild conditions from corresponding aldedyde or ketone and pyrrole. The condensation reactions proceed in dilute HCl at room temperature very fast, and there is no need for elevation of temperature, at which more tripyrromethane **4** and other by-products are formed. By changing molar ratio of starting compounds and by adjustment of reaction mixture concentration, the formation of dipyrromethanes **3** or alternatively tripyrromethanes **4** is controlled. For the course of condensation we can draw following conclusions: low concentrations of starting compounds led to tripyrromethanes **4** as major products, oppositely, high concentrations resulted in preferential formation of dipyrromethanes **3**. Selectivity depends on the nature of carbonyl compound, however, the conclusions for selective **3** or **4** formation given above, seem to be universal. Described synthetic protocol was found to be very cheap, useful, selective, and friendly to environment.

EXPERIMENTAL

Reactions with Cyclodextrines. General Procedure *A*

An aldehyde was added into solution of CD and the mixture was shaken, then pyrrole and aqueous HCl were added. After 20–60 min a solid precipitated (the reaction rate depends on HCl amount). The reaction was quenched by addition of aqueous NH_3, and the solid was filtered off, washed with degassed water and dried quickly in vacuo. By dissolving in dichloromethane traces of remaining CD precipitated and were filtered off, and the solution was used for analyses. The ratio dipyrromethane **3**:tripyrromethane **4** has been calculated from the ^{1}H NMR spectrum of representative sample, and is given as molar ratio. The product purity has been calculated as integral area of meso-proton peaks for **3** and **4** divided by the integral area of whole meso-protons chemical shift area. Conversion has been calculated from

the integral area of meso-protons and the integral area of aldehyde protons. In some cases the conversion has to be calculated based on pyrrole signals.

Reactions Without Cyclodextrines. General Procedure *B*

Pyrrole has been dissolved in dilute aqueous HCl. The solution was stirred and an aldehyde was added. After couple minutes a solid becomes precipitated. The reaction (after 17 h at room temperature, if not specified otherwise) was quenched by aqueous NH_3 and extracted by dichloromethane. The organic layer was dried over $MgSO_4$ and evaporated to dryness. Representative sample of obtained solid (crude product) was used for NMR analysis (as described in procedure *A*) or for isolation of dipyrromethane **3** or tripyrromethane **4**.

Preparation of Dipyrromethane **3c** and Tripyrromethane **4c**

According to general procedure *B*, 0.4 ml (5.8 mmol) of pyrrole, 144 mg (0.95 mmol) of 4-nitrobenzaldehyde, and 80 ml of dilute aqueous HCl (1:99) were used. The crude product was separated on preparative TLC to obtain 203 mg (80%) of dipyrromethane **3c** and 10 mg (4%) of tripyrromethane **4c**. The NMR data of dipyrromethane are identical with published ones[23]. The NMR data of **3c**: ^{1}H NMR (300 MHz, $CDCl_3$): 8.10 (m, 6 H); 8.01 (m, 4 H); 6.75 (td, 2 H, 2.7, 1.5); 6.16 (dt, 2 H, 3.3, 2.7); 5.85 (m, 2 H); 5.73 (dd, 2 H, 2.7, 0.6); 5.50 (s, 2 H). LR-MS (FAB$^+$): for $C_{16}H_{17}N_2$ (MH^+) calculated 237.14; found: 237.20.

Preparation of Dipyrromethane **3f**

According to general procedure *B*, 33.6 g (0.50 mol) of pyrrole, 20 g (0.17 mol) of acetophenone, and 15 ml of concentrated aqueous HCl in 1 l of water were used. The crude product was separated by column chromatography (200 g of silica, dichloromethane) to obtain 33.2 g (85%) of dipyrromethane **3f**. The NMR data of **3f** are identical with published ones[20].

Preparation of Tripyrromethane **4a**

According to general procedure *B*, 98 µl (1.4 µmol) of pyrrole, 95 µl (0.9 µmol) of benzaldehyde (**1a**), and 800 ml of dilute aqueous HCl (1:99) were used. The crude product was separated by column chromatography (40 g of silica, dichloromethane) to obtain 81 mg (48%) of tripyrromethane **4a**. The NMR data of **4a** are identical with published ones[14].

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