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# Green protection of pyrazole, thermal isomerization and deprotection of tetrahydropyranylpyrazoles, and high-yield, one-pot synthesis of 3(5)-alkylpyrazoles†

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We report a new synthetic approach that opens up the possibility of large scale, one-pot pyrazole derivatization by a wide variety of functionalities, including alkyl, halogen, hydroxyl, amino, azido, carbonyl, and organo-element (e.g., B, Si, P) groups. The approach is illustrated by the highly efficient synthesis of fourteen 3(5)-alkylpyrazoles, including the novel isopentyl- and *n*-hexadecyl derivatives, as well as 1,6-bis(pyrazol-3(5)-yl)hexane. The value of the new approach lies in the discovery of a green (solvent- and catalyst-free, quantitative) protection of pyrazole, followed by a high-yield lithiation/alkylation/deprotection sequence in the same pot. For the first time, the corresponding *N*-tetrahydropyran-2-yl (THP) intermediates have been isolated and characterized. Thermal isomerization of the 5-alkyl-1-(THP) to the 3-alkyl-1-(THP) isomer is shown to be an advantageous, green alternative to the acid-catalyzed, sequential protecting-group switching methodology in pyrazole chemistry. The X-ray crystal structures of 1,6-bis(pyrazol-3(5)-yl)hexane and 5-*n*-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole reveal supramolecular architectures that shine light on the remarkable affinity for water and unexpected insolubility in organic solvents of alkylene-bridged bis(pyrazoles). 3(5)-Alkylpyrazoles are obtained in high yield from pyrazole by a one-pot procedure.

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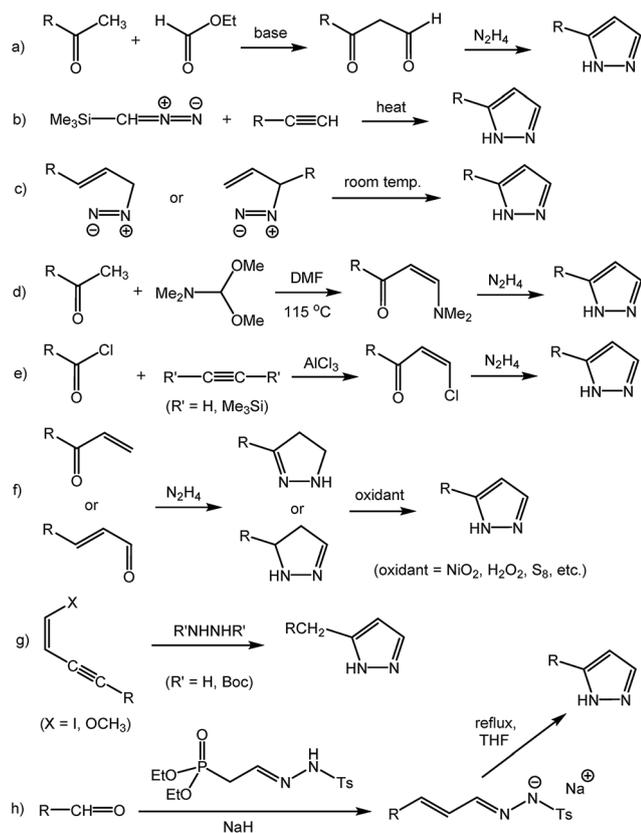
## 1. Introduction

Pyrazole, a five-membered aromatic heterocycle with two adjacent nitrogen atoms (1,2-diazole), is a remarkably versatile moiety with a wide range of applications. Pyrazole-based molecules can be found in living organisms: currently, at least sixteen natural products containing the pyrazole moiety are known.<sup>1</sup> 3(5)-Nonylpyrazole, the first pyrazole-containing natural product derivative obtained in 1954, has the strongest antibiotic activity among 3(5)-alkylpyrazoles.<sup>2</sup> 4-Methylpyrazole is an effective antidote for methanol and ethylene glycol poisoning.<sup>3</sup> A remarkably broad range of medicinal products (including anti-inflammatory, antitumor, antihypertensive, anticoagulant, antimicrobial, antiviral, anticonvulsant, antidepressant drugs), as well as agricultural chemicals (insecticides, fungicides, herbicides) and dyes (including food colorings), are pyrazole derivatives.<sup>4</sup> Pyrazole-based ligands are also intensively used in various areas of coordination and materials chemistry.<sup>5</sup>

In light of the widespread interest in pyrazole derivatives, we herein present a novel, straightforward and efficient synthesis of 3(5)-alkylpyrazoles, which offers valuable advantages over the currently used methods. 3(5)-Alkylpyrazoles are most commonly synthesized by the two archetypal pyrazole synthesis methods of Knorr<sup>6</sup> and Pechmann.<sup>7</sup> In a typical Knorr pyrazole synthesis, a  $\beta$ -ketoaldehyde (or the corresponding acetal/ketal), prepared from ethyl (or methyl) formate and a ketone, is condensed with hydrazine (Scheme 1a).<sup>2,8</sup> The Pechmann pyrazole synthesis consists of the 1,3-dipolar cycloaddition of diazomethane to alkynes (Scheme 1b).<sup>9,10</sup> 3-Diazoalkenes spontaneously undergo intramolecular 1,3-dipolar cycloaddition to yield 3(5)-alkylpyrazoles (Scheme 1c).<sup>11</sup> Other common routes to 3(5)-alkylpyrazoles free of 4-alkyl or 3,5-dialkyl side products include the conversion of a ketone to a  $\beta$ -(dimethylamino)vinyl ketone using *N,N*-dimethylformamide dimethyl acetal (Scheme 1d),<sup>10</sup> or of an acyl chloride to a  $\beta$ -chlorovinyl ketone using acetylene (or its bis-trimethylsilyl derivative, Scheme 1e),<sup>12</sup> followed in both cases by reaction with hydrazine. Enones or enals result in 2-pyrazolines upon reaction with hydrazine,<sup>10,13</sup> which can be converted to the corresponding pyrazoles by oxidation (Scheme 1f).<sup>10,14</sup> Alternatively, the corresponding ynones or ynals (Scheme 1f, alkyne instead of alkene) yield 3(5)-alkylpyrazoles directly upon treatment with hydrazine.<sup>15</sup> Iodo-<sup>16</sup> or methoxy-enynes<sup>17</sup> (Scheme 1g) also form 3(5)-alkylpyrazoles with

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† Electronic supplementary information (ESI) available: <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of all intermediates and final products, CIF files for 1,6-bis(pyrazol-3(5)-yl)hexane hydrate and 5-*n*-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole. CCDC 1040198 and 1040199. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra00837a



Scheme 1 Current strategies for the synthesis of 3(5)-alkylpyrazoles (R = alkyl group).

hydrazine. Aldehydes can be transformed into 3(5)-alkylpyrazoles *via*  $\alpha,\beta$ -unsaturated tosylhydrazones (Scheme 1h).<sup>18</sup> All these methods present a number of shortcomings, including the need for not readily available and/or expensive starting materials or reagents (which often require additional synthesis and purification steps), highly toxic and/or potentially explosive reagents (diazomethane and derivatives, hydrazine), and low overall yields.

## 2. Results and discussion

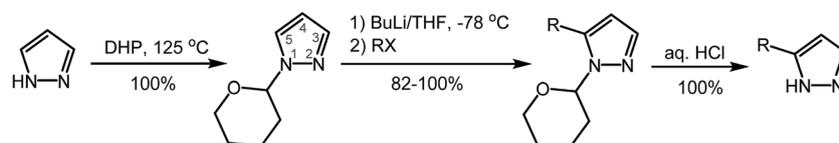
### 2.1. Green pyrazole protection

Herein we describe a pyrazole 3(5)-C-alkylation method that employs inexpensive 1*H*-pyrazole and 1-haloalkanes as starting materials, *via* a lithiated pyrazole intermediate (Scheme 2). Since C-alkylation requires protection of the pyrazole NH nitrogen (to avoid N-alkylation), a facile and efficient protection and deprotection method, using an inexpensive protecting

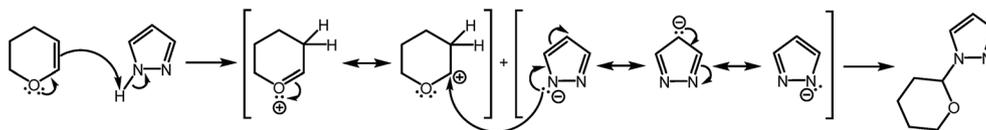
group that will not undergo lithiation itself with <sup>n</sup>BuLi, is needed to maximize the overall yield and the value of the method. The tetrahydropyran-2-yl (THP) moiety proves to be an excellent protecting group to this end. The THP protecting group is usually introduced under acidic catalysis (*e.g.*, F<sub>3</sub>CCOOH, *p*-toluenesulfonic acid), followed by work-up/purification involving either vacuum distillation from NaH<sup>19</sup> or column chromatography.<sup>20</sup> We find that the reaction of neat pyrazole with a slight excess of inexpensive 3,4-dihydro-2*H*-pyran (DHP) proceeds without a catalyst at 125 °C to provide 1-(tetrahydropyran-2-yl)pyrazole with 100% conversion (Scheme 3). The excess DHP can easily be removed at the end of the reaction under reduced pressure (b.p. 86 °C at 760 mmHg). Pure THP-protected pyrazole (by <sup>1</sup>H and <sup>13</sup>C NMR) is thus obtained quantitatively under solvent-free conditions, without the need for work-up or purification. The inspiration for this catalyst-free, solventless method originated from the observation that when heated, 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles isomerize to 3-alkyl-1-(tetrahydropyran-2-yl)pyrazoles, a process in which the THP-N bond is thermally cleaved, followed by the formation of a new THP-N bond at the adjacent, sterically less hindered N-atom (*vide infra*). As temperature increases, so does the acidity of the pyrazole N-H proton, eliminating the need for an additional acid catalyst.

### 2.2. Lithiation/alkylation

Lithiation of THP-protected pyrazole with <sup>n</sup>BuLi at -78 °C, followed by the addition of a primary haloalkane, leads to 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles with excellent conversions, as shown by <sup>1</sup>H NMR (Table 1). As expected for S<sub>N</sub>2 nucleophilic substitutions in general, this alkylation works best with least hindered, primary alkyl halides. Indeed, close to quantitative conversions (94–99%) are obtained with 1-iodo- and even with 1-bromoalkanes (except for C<sub>16</sub>). Under identical experimental conditions, secondary alkyl and vinyl iodides provide low conversions (cyclohexyl: 16%; isopropyl: 7%; *sec*-butyl: <1%; vinyl: 7%), and no reaction is observed with *tert*-butyl iodide and iodobenzene. Refluxing the reaction mixture under nitrogen does not provide a significant improvement. Allyl- and benzyl bromides give conversions of 7% and 36%, respectively. Isobutyl iodide (1-iodo-2-methylpropane), although a primary alkyl iodide, also provides a poor conversion (7%), further evidencing that steric crowding around the electrophilic reaction center is a critical limiting factor. Isopentyl iodide (1-iodo-3-methylbutane), in which the branching is one carbon atom further from the reaction center, reacts efficiently, with conversion similar to the *n*-butyl and *n*-pentyl analogs.



Scheme 2 Synthesis of 3(5)-alkylpyrazoles by alkylation of pyrazole (DHP = 3,4-dihydro-2*H*-pyran; R = primary alkyl group; X = I or Br).



Scheme 3 Proposed mechanism of formation of 1-(THP)pyrazole by electrophilic addition of pyrazole to 3,4-dihydro-2H-pyran (DHP).

**2.2.1. Method A.** Initially, the alkylations were carried out with excess (10 mol%) iodoalkane, to maximize the conversion of pyrazole to alkylpyrazole. Excellent conversions are obtained indeed (94–100%, Table 1), and the small amounts (less than 6%) of unreacted 1-(tetrahydropyran-2-yl)pyrazole left behind in the reaction mixture can easily be removed by gentle heating under reduced pressure. The excess 1-iodoalkane (up to C<sub>7</sub>) can also be removed under similar conditions, at temperatures that do not affect the product. The removal of the higher iodoalkanes, however, becomes increasingly more difficult as their boiling point increases, and the higher temperatures needed for the distillation (under reduced pressure) of C<sub>8</sub> and longer iodoalkanes lead to isomerization of the product and even loss of the protecting group. While this is not a problem if the target is the preparation of unprotected 3(5)-alkylpyrazoles, the isolation of pure THP-protected alkylpyrazoles (C<sub>8</sub> and up) has to be performed by column chromatography. Pure 5-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole is obtained, for example, by elution with hexane/ethyl acetate (6 : 1) on a silica gel column.

**2.2.2. Method B.** To simplify the purification of THP-protected alkylpyrazoles (C<sub>8</sub> and up) and eliminate the need for chromatography, we next carried out alkylations with excess (10 mol%) 1-(tetrahydropyran-2-yl)pyrazole, instead of excess iodoalkane. In this case, the iodoalkane is completely consumed during the reaction (except for C<sub>16</sub>), and the excess unreacted 1-(tetrahydropyran-2-yl)pyrazole is readily removed by heating to 55–60 °C under reduced pressure (0.1–0.2 mmHg) (Table 1: entries 11, 13, 15, 18, 20, 21).

A search of the literature reveals only two isolated reports when 3(5)-alkylpyrazoles were prepared directly from pyrazole: 3(5)-methylpyrazole (55% yield)<sup>21</sup> and 3(5)-*n*-butylpyrazole (41% yield).<sup>22</sup> The relatively low yields are partly due to the competing lithiation/alkylation of the protecting groups used in those two cases, 1-pyrrolidinomethyl<sup>21</sup> and 4-methoxybenzyl,<sup>22</sup> respectively. The tetrahydropyran-2-yl protecting group is inert under our working conditions, and reactivity at the pyrazole 5-position (adjacent to the protecting group, Scheme 2) is observed exclusively. Similarly, only 3-methyl-1-(tetrahydropyran-2-yl)pyrazole and not 5-methyl-1-(tetrahydropyran-2-yl)pyrazole can be deprotonated with <sup>n</sup>BuLi under identical conditions.<sup>23</sup> Although the presence of the oxygen heteroatom (donor) in THP might facilitate lithiation<sup>24</sup> through the “complex induced proximity effect” (CIPE),<sup>25</sup> it has been noted earlier (without explanation) that lithiation by <sup>n</sup>BuLi of 1-methyl- or 1-phenylpyrazole, where CIPE is absent, likewise does not occur at the 3-position.<sup>26</sup> The reason for the observed reactivity is presumably the repulsion between the lone pair of electrons of the carbanion formed upon deprotonation and the one of the adjacent nitrogen atom

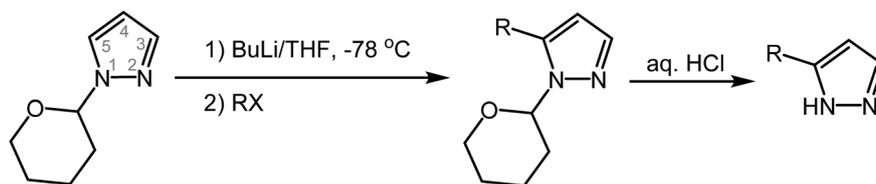
(Scheme 4). A similar phenomenon was later observed in a related imidazole system, and was termed “adjacent lone pair effect”.<sup>27</sup> More recent experimental measurements, as well as computational studies confirm the significantly higher acidity of the proton in the 5-position than the one in the 3-position in 1-methylpyrazole<sup>28</sup> and 1-arylpyrazoles (pK<sub>a</sub> difference of ~7 for the latter).<sup>29</sup>

### 2.3. Thermal isomerization and deprotection of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles

As mentioned above, the small amounts of unreacted 1-(tetrahydropyran-2-yl)pyrazole can be removed from the reaction mixture by heating to 55–60 °C in vacuum (0.10–0.20 mmHg). When alkyl = methyl, ethyl, *n*-propyl, *n*-butyl and *i*-pentyl, the excess iodoalkane can be removed as well, at temperatures well below the boiling point of the corresponding THP-protected pyrazoles. The latter can be distilled unaffected within a temperature range of 71–100 °C at 0.10–0.20 mmHg (see Experimental section). In the case of the *n*-pentyl, *n*-hexyl and *n*-heptyl derivatives, the corresponding excess iodoalkanes can be completely removed by heating to 55–60 °C under vacuum; however, distillation of the products at 104–106 °C (0.10 mmHg), 121–123 °C (0.20 mmHg) and 128–130 °C (0.15 mmHg), respectively, leads to isomerization (Scheme 5), and provides a mixture of the 5-alkyl and 3-alkyl isomers in a 64/36, 56/44 and 38/62 molar ratio, respectively, as determined by <sup>1</sup>H NMR. In the case of *n*-octyl and longer *n*-alkyl derivatives, the excess 1-iodoalkane can no longer be removed from the reaction mixture by vacuum distillation (at 0.10–0.20 mmHg) without affecting the product: heating to a temperature at which the corresponding 1-iodoalkane vaporizes does not only lead to isomerization, but also to partial or even complete loss of the protecting group. For example, in the case of the *n*-octyl derivative, isomerization and partial deprotection occur at 80 °C, well below its boiling point (110–130 °C at 0.20 mmHg), at which extensive deprotection is observed. Loss of the tetrahydropyranyl group from THP-protected hydroxyl- or carboxylic acid-functionalized polymers at high temperatures has been reported.<sup>30</sup>

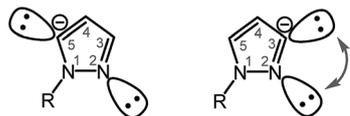
Thermal isomerization occurs not only for 5-alkyl derivatives with longer alkyl chains, but also for the ones with short alkyl groups (and presumably even for the parent 1-(tetrahydropyran-2-yl)pyrazole), although at more elevated temperatures. For example, in the case of 5-methyl-1-(tetrahydropyran-2-yl)pyrazole, thermal isomerization at 125 °C in a pressure tube yields 32 mol% 3-methyl isomer after 24 hours, and 77 mol% 3-methyl isomer after 48 hours. No further change occurs after

**Table 1** Synthesis of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles and 3(5)-alkylpyrazoles by alkylation of THP-protected pyrazole. Conversion is based on the ratio of integrated  $^1\text{H}$  NMR signals of the product and the residual limiting reactant (THP-protected pyrazole for Method A; haloalkane for Method B) in the crude reaction mixture

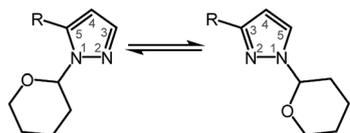


| Entry | Halide reactant (RX) (Method) | Protected pyrazole |                    | Pyrazole | Pyrazole       |                    |
|-------|-------------------------------|--------------------|--------------------|----------|----------------|--------------------|
|       |                               | Conversion (%)     | Isolated yield (%) |          | Conversion (%) | Isolated yield (%) |
| 1     | Iodomethane (A)               | 100                | 99                 |          | 100            | 94                 |
| 2     | Iodoethane (A)                | 99                 | 89                 |          | 100            | 97                 |
| 3     | Bromoethane (A)               | 96                 | 90                 |          |                |                    |
| 4     | 1-Iodopropane (A)             | 95                 | 90                 |          | 100            | 99                 |
| 5     | 1-Iodobutane (A)              | 96                 | 95                 |          | 100            | 92                 |
| 6     | 1-Iodopentane (A)             | 94                 | 88                 |          | 100            | 89                 |
| 7     | 1-Iodo-3-methylbutane (A)     | 94                 | 91                 |          | 100            | 99                 |
| 8     | 1-Iodohexane (A)              | 96                 | 96                 |          | 100            | 95                 |
| 9     | 1-Bromohexane (A)             | 96                 | 92                 |          |                |                    |
| 10    | 1-Iodoheptane (A)             | 96                 | 91 <sup>a</sup>    |          | 100            | 98                 |
| 11    | 1-Iodoheptane (B)             | 100                | 98                 |          |                |                    |
| 12    | 1-Iodooctane (A)              | 96                 | 89 <sup>a</sup>    |          | 100            | 99                 |
| 13    | 1-Iodooctane (B)              | 100                | 92                 |          |                |                    |
| 14    | 1-Iodononane (A)              | 95                 | 92 <sup>a</sup>    |          | 100            | 99                 |
| 15    | 1-Iodononane (B)              | 100                | 88                 |          |                |                    |
| 16    | 1-Bromodecane (A)             | 96                 | 91                 |          | 100            | 94                 |
| 17    | 1-Iodododecane (A)            | 95                 | Not isolated       |          | 100            | 99                 |
| 18    | 1-Iodododecane (B)            | 100                | 92                 |          |                |                    |
| 19    | 1-Iodohexadecane (A)          | 84                 | 76                 |          | 100            | 99                 |
| 20    | 1-Iodohexadecane (B)          | 82                 | Not isolated       |          |                |                    |
| 21    | 1,6-Diiodohexane (B)          | 100                | 80                 |          | 100            | 84                 |

<sup>a</sup> Mixture of 5-alkyl and 3-alkyl isomers.



**Scheme 4** Deprotonation of the 3-position of N-protected pyrazoles is unfavorable, due to the electrostatic repulsion between the lone pair of electrons of the resulting carbanion, and the lone pair of N in the adjacent 2-position (R = protecting group).



**Scheme 5** Thermal isomerization of 5-alkyl-1-(THP)pyrazoles to 3-alkyl-1-(THP)pyrazoles (R = alkyl).

heating for 84 hours, indicating that equilibrium between the 5- and 3-methyl isomers is reached at a 23 : 77 molar ratio.

As discussed above, only 3-alkyl-1-(THP)pyrazoles and not 5-alkyl-1-(THP)pyrazoles can be lithiated by <sup>n</sup>BuLi, if further derivatization of the pyrazole nucleus is desired. Therefore, the conversion of 5-alkyl- to 3-alkyl isomers is an important step for synthetic purposes. Pyrazole protecting-group switching is currently performed by acid-catalyzed, sequential deprotection–reprotection.<sup>20</sup> Direct protecting group switching, under acidic catalysis, has also been reported.<sup>31</sup> Thermal isomerization, presented herein, offers a new *green* alternative, which eliminates the need for solvents, additional reagents and work-up.

#### 2.4. Acid-catalyzed deprotection of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles

Complete deprotection of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles can easily be achieved at ambient conditions, using an aqueous HCl solution, leading to pure 3(5)-alkylpyrazoles in near quantitative yields after standard work-up (Table 1).

#### 2.5. One-pot synthesis

The virtually quantitative conversion of the steps described above allows for three steps (protection, lithiation/alkylation, deprotection) to be performed sequentially in one pot, with no need for separation and purification of the intermediates. Thus, 3(5)-alkylpyrazoles can be prepared from pyrazole in excellent yields (see Experimental section).

#### 2.6. Crystallographic studies

The unexpected insolubility of 1,6-bis(pyrazol-3(5)-yl)hexane in most common solvents, as well as the difficulty in completely removing water from it, even after heating in high vacuum, prompted us to carry out single-crystal X-ray diffraction studies to elucidate its solid state structure.

Within the crystal lattice of 1,6-bis(pyrazol-3(5)-yl)hexane, the bridging hexylene unit is fully extended and the two pyrazole moieties are at a dihedral angle of 63.9(1)° (Fig. 1). The pyrazole N–H hydrogen atoms are located on the N-atom adjacent to the bridging hexylene unit, and are involved in hydrogen-bonding with the solvent water molecule (Table 2). The two H-atoms of H<sub>2</sub>O, in turn, are involved in hydrogen-bonding to the other pyrazole N-atom. Besides the hydrogen-bonded network within the resulting two-dimensional layer (Fig. 2), edge-to-face interactions are observed between neighboring pyrazole (pz) units, with closest contact of 2.961(3) Å (C11–H11⋯N2'), C11–H11⋯centroid (pz) distance of 3.183(3) Å, centroid (pz)–centroid (pz) distance of 5.262(2) Å, and pz–pz dihedral angle of 63.9(1)°. Further edge-to-face pyrazole interactions are observed in-between the layers (Fig. 3), with closest contact of 2.901(4) Å (C2–H2⋯C12'), C2–H2⋯centroid (pz) distance of 3.169(3) Å, centroid (pz)–centroid (pz) distance of 5.159(2) Å, and pz–pz dihedral angle: 63.9(1)°. Such a 2D layered structure is unusual for NH–pyrazoles with no additional donor atoms, which typically self-assemble either into discrete cyclic motifs (dimers, trimers, tetramers, hexamers), or 1D catemers, *via* intermolecular N–H⋯N hydrogen bonds.<sup>32</sup>

1,6-Bis(pyrazol-3(5)-yl)hexane is only soluble in highly polar solvents, such as methanol, ethanol, dimethylformamide, dimethylsulfoxide, nitromethane and nitrobenzene, and is slightly soluble in cold water (solubility increases significantly in hot water). Its very poor solubility in other organic solvents (isopropanol, acetonitrile, ethyl acetate, acetone, tetrahydrofuran, diethyl ether, dichloromethane, chloroform, hydrocarbons), even at reflux temperatures, is surprising, given that 3(5)-propylpyrazole (half of the 1,6-bis(pyrazol-3(5)-yl)hexane molecule) is readily soluble in all common solvents, including hexane. The water of crystallization provides increased lattice enthalpy, by forming an extended hydrogen-bonded 2D network with the 1,6-bis(pyrazol-3(5)-yl)hexane units, which concurs with the difficulty in drying 1,6-bis(pyrazol-3(5)-yl)hexane. Furthermore, the extensive H-bonding interactions within the lattice are in accord with the poor solubility of the compound in solvents of medium or low polarity. THP-protected 1,6-bis(pyrazol-3(5)-yl)hexane, which lacks the N–H hydrogen bond donor, is readily soluble in common organic solvents (even in hexane, slightly), and similarly to all other 3(5)-alkylpyrazoles studied here, it does not have affinity for water.

Two crystallographically independent molecules are found within the asymmetric unit of 5-*n*-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole (Fig. 4). The C<sub>16</sub> chains are fully extended, a common feature of crystal structures of molecules possessing long hydrocarbon chains. An analysis of the Cambridge Structural Database reveals that it is the ratio between the size/number of the aliphatic chains and the size of the polar part of the molecule/structure that determines the conformation of the chain. When the size of the chain(s) dominates, a fully extended conformation of the chain, which maximizes the London dispersion forces between neighboring chains, provides a significant contribution to the overall crystal lattice enthalpy. The result is a layered structure, wherein the non-

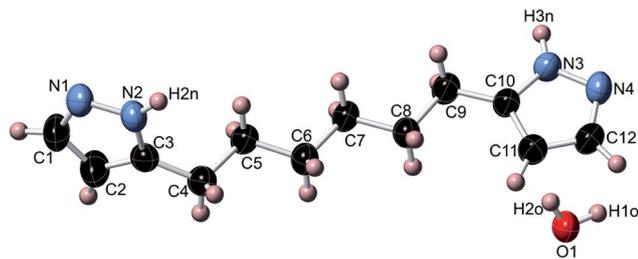


Fig. 1 Crystal structure (thermal ellipsoid plot, 50% probability level) of 1,6-bis(pyrazol-3(5)-yl)hexane hydrate.

polar chains and the more polar part of the molecule each aggregate separately to form alternating 2D layers (Fig. 5). When the size of the polar part of the molecule (which might include counterions) dominates, the long hydrophobic chains might not be fully extended and densely packed, but can assume different bent conformations to fill the crystal lattice voids determined by the dominant polar interactions.<sup>33</sup>

### 3. Summary

The known synthetic strategies for the synthesis of 3(5)-alkylpyrazoles involve highly toxic and potentially explosive reagents, expensive starting materials, or long synthetic schemes with low overall yields, which render the synthesis of 3(5)-alkylpyrazoles expensive, often inefficient, and not readily scalable. Herein we present a novel one-pot strategy based on inexpensive and readily available starting materials (1*H*-pyrazole, haloalkanes) and reagents (3,4-dihydro-2*H*-pyran, <sup>n</sup>BuLi, aqueous HCl) that is easily scalable and eliminates additional intermediate synthesis and purification steps, provides high yields and minimizes waste production. We developed a new solventless, catalyst-free method for the protection of pyrazole, which needs no work-up or purification and is amenable for large-scale production, offering a truly green protection technique for 1*H*-pyrazole and its derivatives. Since 1-bromoalkanes were found to give similar conversions to 1-iodoalkanes (for C<sub>1</sub>–C<sub>12</sub>), we conclude that the use of the former is preferable, for they are less expensive, have lower boiling points allowing an easier removal of excess amounts from reaction mixtures (method A), and eliminate the need for washing with thiosulfate solution (to remove traces of iodine formed by oxidation of iodide by air, when 1-iodoalkanes are used as starting materials). In the case of longer alkyl derivatives, the use of excess 1-(tetrahydropyran-2-yl)pyrazole is preferable (method B), which is easier to remove under reduced pressure than the long-chain haloalkanes.

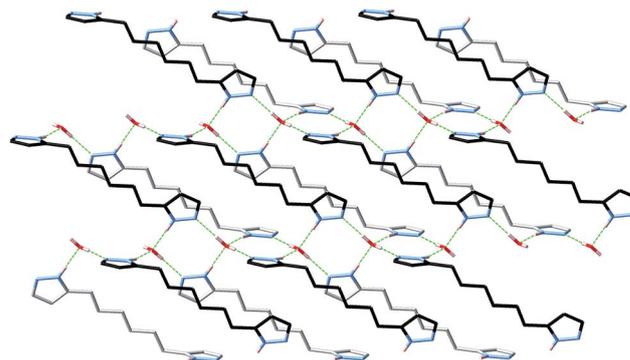


Fig. 2 Hydrogen-bonding network (green dashed lines) within a layer of 1,6-bis(pyrazol-3(5)-yl)hexane hydrate.

We have shown that protecting-group switching (5-alkyl-1-(THP)pyrazole to 3-alkyl-1-(THP)pyrazole conversion) can be accomplished by simple, catalyst- and solvent-free thermal isomerization. The isomerization equilibrium favors the sterically less hindered 3-alkyl-1-THP isomer, and the ratio of 3-alkyl- vs. 5-alkyl-1-THP isomer increases with increasing alkyl chain length. Also, larger alkyl groups render the N-THP bond more labile, and as a result, isomerization (and even deprotection) occurs at lower temperatures.

We illustrated the utility of the new one-pot method by synthesizing and characterizing a series of 3(5)-alkylpyrazoles (C<sub>1</sub>–C<sub>10</sub>, C<sub>12</sub>), including the novel isopentyl- and *n*-hexadecyl derivatives, as well as 1,6-bis(pyrazol-3(5)-yl)hexane, and their corresponding *N*-tetrahydropyran-2-yl derivatives. The method has a wide scope, as other electrophiles, such as halogens, oxygen, tosyl azide, various carbonyl-containing compounds and organoelement (B, Si, P, *etc.*) reagents can be employed instead of alkyl halides, offering a wide variety of pyrazole derivatives for the pharmaceutical industry, agricultural applications and coordination/materials chemistry.

## 4. Experimental section

### 4.1. General

THF was dried with Na/benzophenone and freshly distilled under nitrogen prior to use. All other commercial reagents and solvents were used as received. Vacuum was measured with a McLeod gauge connected to a Schlenk line. Melting points were determined on a MEL-TEMP II (Laboratory Devices, USA) apparatus. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at room temperature on a Jeol JNM-ECP400 instrument. High-resolution

Table 2 Summary of hydrogen bonding data for 1,6-bis(pyrazol-3(5)-yl)hexane hydrate (with esds, except fixed/riding hydrogens)

| D–H⋯A      | D–H (Å) | H⋯A (Å) | D⋯A (Å)  | D–H–A (°) | Symmetry operator for A  |
|------------|---------|---------|----------|-----------|--------------------------|
| O1–H1o⋯N4' | 0.86(2) | 1.95(2) | 2.807(3) | 175(2)    | $-x + 1, -y + 2, -z + 1$ |
| O1–H2o⋯N1' | 0.84(2) | 1.98(2) | 2.818(3) | 177(3)    | $-x, -y, -z + 1$         |
| N2–H2n⋯O1' | 0.86    | 1.97    | 2.826(2) | 171       | $x, y - 1, z$            |
| N3–H3n⋯O1' | 0.86    | 1.98    | 2.838(3) | 175       | $x + 1, y, z$            |

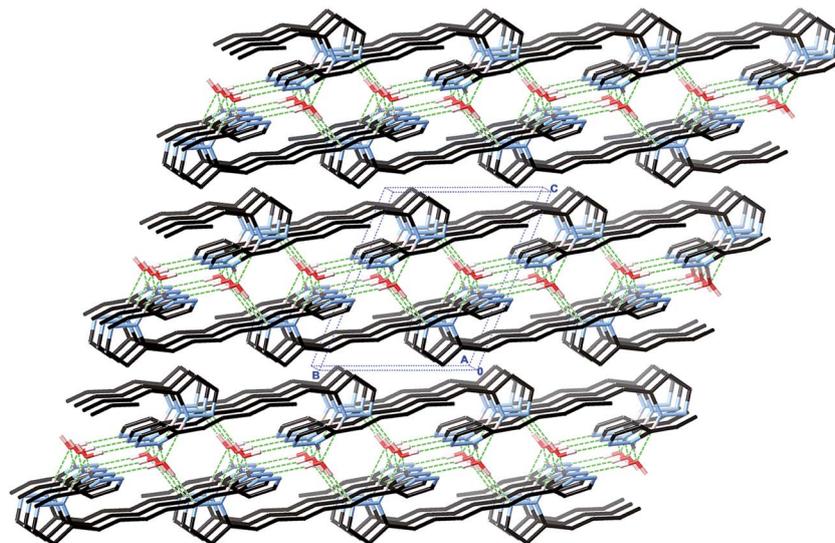


Fig. 3 View of the layered structure of 1,6-bis(pyrazol-3(5)-yl)hexane hydrate (H-bonds shown by green dashed lines).

mass spectra were obtained with a Waters Synapt G1 HDMS instrument, using an electrospray ionization source (negative mode for pyrazoles, positive mode for THP-protected pyrazoles).

#### 4.2. Synthesis of 1-(tetrahydropyran-2-yl)pyrazole (1)

A heavy-wall glass pressure flask was charged with pyrazole (50.0 g, 73.4 mmol) and 3,4-dihydro-2H-pyran (68.2 g, 81.1 mmol). The mixture was homogenized and then heated to 125 °C for 24 hours in an oven. After cooling to room temperature, the product was subjected to vacuum to remove traces of excess DHP. Pure THP-protected pyrazole (as indicated by  $^1\text{H}$  and  $^{13}\text{C}$  NMR) is obtained in quantitative yield (111 g). The product can be distilled at 64–65 °C (0.08 mmHg), if further purification is desired.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 7.60 (d, 1H,  $^3J = 2.2$  Hz, 5-*H*-pz), 7.55 (s, 1H, 3-*H*-pz), 6.29 (m, 1H, 4-*H*-pz), 5.38 (dd, 1H,  $^3J = 9.9$  Hz,  $^3J = 2.6$  Hz, *CH*-THP), 4.02–4.07 (m, 1H,  $\text{CH}_2\text{O}$ -THP), 3.65–3.73 (m, 1H,  $\text{CH}_2\text{O}$ -THP), 1.97–2.19 (m, 3H,  $\text{CH}_2$ -THP),

1.55–1.76 (m, 3H,  $\text{CH}_2$ -THP) ppm.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ): 7.86 (d, 1H,  $^3J = 2.2$  Hz, 5-*H*-pz), 7.48 (s, 1H, 3-*H*-pz), 6.30 (s, 1H, 4-*H*-pz), 5.39 (dd, 1H,  $^3J = 9.9$  Hz,  $^3J = 2.6$  Hz, *CH*-THP), 3.88–3.95 (m, 1H,  $\text{CH}_2\text{O}$ -THP), 3.57–3.67 (m, 1H,  $\text{CH}_2\text{O}$ -THP), 2.03–2.14 (m, 1H,  $\text{CH}_2$ -THP), 1.85–1.97 (m, 2H,  $\text{CH}_2$ -THP), 1.58–1.72 (m, 1H,  $\text{CH}_2$ -THP), 1.48–1.58 (m, 2H,  $\text{CH}_2$ -THP) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ): 139.7, 127.6, 106.1, 87.6, 67.9, 30.6, 25.0, 22.6 ppm.

#### 4.3. General procedure for the preparation of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles (2–15)

Method A: 1-(tetrahydropyran-2-yl)pyrazole (5.000 g, 32.85 mmol) is dissolved in anhydrous THF (50 mL) in a Schlenk flask under a dry  $\text{N}_2$  atmosphere. The solution is chilled to  $-78$  °C by stirring for 15 minutes in a dry-ice/isopropanol bath.  $n\text{BuLi}$  (1.6 M in hexane, 21 mL, 32.85 mmol) is added dropwise from an  $\text{N}_2$ -purged syringe. Stirring at  $-78$  °C is

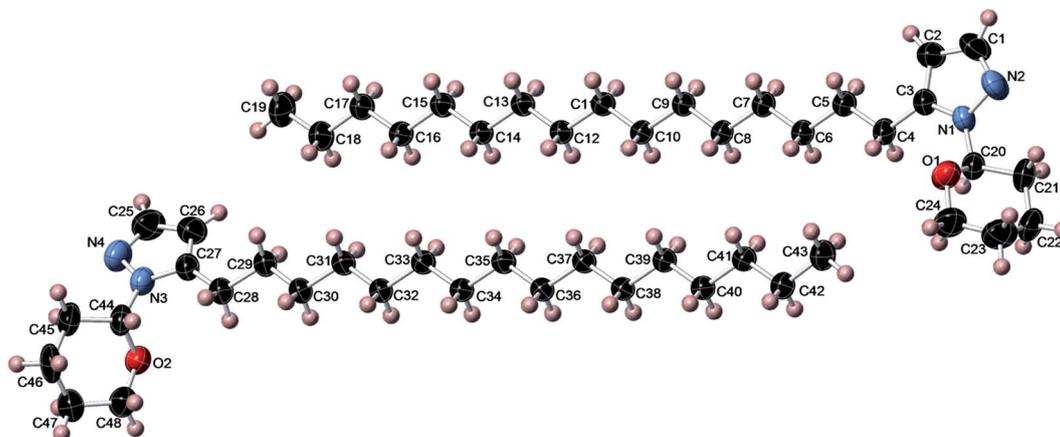


Fig. 4 Crystal structure (thermal ellipsoid plot, 50% probability level) of 5-*n*-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole, showing the two crystallographically independent molecules (from different asymmetric units, for clarity).

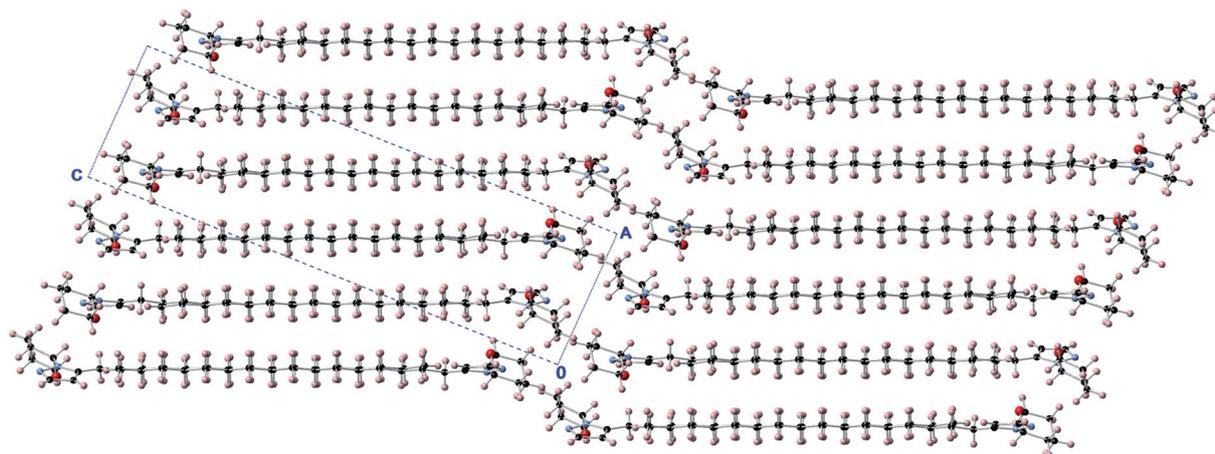


Fig. 5 Packing diagram of 5-*n*-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole (view down the *b* axis), showing a layered structure.

continued for another 30 minutes, then the 1-iodo- or 1-bromoalkane (36.14 mmol; in the case of 1,6-diiodohexane: 10.95 mmol) is added dropwise over 20 minutes. After stirring at  $-78\text{ }^{\circ}\text{C}$  for 3 hours, the solution is left to warm up to room temperature and is quenched with water (1 mL). The volatiles are removed on a Rotavap, 80 mL water is added to the residue and it is extracted with ethyl acetate (or diethyl ether) ( $3 \times 80\text{ mL}$ ), followed by washing with a 10% aqueous sodium thiosulfate solution (80 mL; only when 1-iodoalkane is used as starting material), brine (80 mL) and drying with anhydrous  $\text{MgSO}_4$ . After removing the volatiles on the Rotavap, the residual oil is heated to  $\sim 75\text{ }^{\circ}\text{C}$  (only when alkyl is  $\text{C}_1\text{--C}_6$ ) under high vacuum ( $\sim 0.15\text{ mmHg}$ ) to remove traces of the unreacted

1-(tetrahydropyran-2-yl)pyrazole and excess 1-haloalkane. Pure 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles (by  $^1\text{H}$  and  $^{13}\text{C}$  NMR) are thus obtained. When alkyl is  $\text{C}_1\text{--C}_4$ , the products can be distilled in vacuum, if needed. When alkyl is  $\text{C}_5$  and longer, distillation leads to isomerization and/or deprotection. In those cases, purification is accomplished by column chromatography (see example for  $\text{C}_{16}$  below). 1,6-Bis(1-(tetrahydropyran-2-yl)pyrazol-5-yl)hexane is purified by recrystallization from ethyl acetate/hexane. The products are colorless oils ( $\text{C}_1\text{--C}_9$ ) or colorless crystalline solids ( $\text{C}_{10}$ ,  $\text{C}_{12}$ ,  $\text{C}_{16}$ , 1,6-bis(1-(tetrahydropyran-2-yl)pyrazol-5-yl)hexane). For conversion calculations, distinct proton signals in the  $^1\text{H}$  NMR spectrum are used: 3-*H*-pyrazole, 4-*H*-pyrazole or *CH*-THP signals for

Table 3 Crystallographic data

|   | $\text{Hpz}(\text{CH}_2)_6\text{pzH} \cdot \text{H}_2\text{O}$ | $\text{CH}_3(\text{CH}_2)_{15}\text{pzTHP}$    |
|---|--|--|
| Formula                                   | $\text{C}_{12}\text{H}_{20}\text{N}_4\text{O}$                 | $\text{C}_{24}\text{H}_{44}\text{N}_2\text{O}$ |
| FW ( $\text{g mol}^{-1}$ )                | 236.32   | 376.61   |
| Crystal system                            | Triclinic  | Triclinic                                      |
| Space group                               | $\text{P}\bar{1}$  | $\text{P}\bar{1}$                              |
| <i>a</i> ( $\text{\AA}$ )                 | 8.8013(4)  | 8.7407(5)                                      |
| <i>b</i> ( $\text{\AA}$ )                 | 9.2025(4)  | 9.4611(5)                                      |
| <i>c</i> ( $\text{\AA}$ )                 | 10.1004(5)   | 29.7000(15)                                    |
| $\alpha$ (deg)                            | 107.833(3)   | 92.436(3)                                      |
| $\beta$ (deg)                             | 93.710(4)  | 91.591(3)                                      |
| $\gamma$ (deg)                            | 114.352(3)   | 104.178(3)                                     |
| <i>V</i> ( $\text{\AA}^3$ )               | 692.06(6)  | 2377.3(2)                                      |
| Crystal size                              | $0.07 \times 0.15 \times 0.40$                                 | $0.10 \times 0.35 \times 0.70$                 |
| <i>Z</i>                                  | 2  | 4  |
| $D_{\text{calc}}$ ( $\text{g cm}^{-3}$ )  | 1.134  | 1.052  |
| $\mu$ ( $\text{mm}^{-1}$ )                | 0.076  | 0.063  |
| $\theta$ Range (deg)                      | 2.60–24.12   | 2.01–34.60                                     |
| Reflns. collected                         | 13 883   | 60 311   |
| Obsd. reflns. [ $I > 2\sigma(I)$ ]        | 1433   | 5456   |
| Data/restraints/parameters                | 2194/2/160   | 8085/0/489                                     |
| GOF (on $F^2$ )                           | 0.956  | 1.015  |
| R factor [ $I > 2\sigma(I)$ ]             | $R_1 = 0.0473$ , $wR_2 = 0.1275$                               | $R_1 = 0.0422$ , $wR_2 = 0.1055$               |
| R factor (all data)                       | $R_1 = 0.0835$ , $wR_2 = 0.1577$                               | $R_1 = 0.0696$ , $wR_2 = 0.1253$               |
| Maximum peak/hole ( $\text{e \AA}^{-3}$ ) | 0.128/−0.185   | 0.134/−0.126                                   |

Method A, and R-CH<sub>2</sub>-X (R = alkyl, X = I or Br) signals for Method B.

Method B: same as Method A, except that 1-(tetrahydropyran-2-yl)pyrazole is used in 10% excess instead of the iodoalkane.

**4.3.1. 5-Methyl-1-(tetrahydropyran-2-yl)pyrazole (2).** B.p. 71–72 °C (0.08 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.43 (d, 1H, <sup>3</sup>J = 1.3 Hz, 3-*H*-pz), 6.03 (d, 1H, <sup>3</sup>J = 1.5 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz, *CH*-THP), 4.00–4.05 (m, 1H, CH<sub>2</sub>O-THP), 3.61–3.68 (m, 1H, CH<sub>2</sub>O-THP), 2.42–2.52 (m, 1H, CH<sub>2</sub>-THP), 2.34 (s, 3H, CH<sub>3</sub>), 2.06–2.14 (m, 1H, CH<sub>2</sub>-THP), 1.92–2.00 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.77 (m, 3H, CH<sub>2</sub>-THP) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 139.1, 106.2, 84.5, 67.8, 29.4, 25.1, 22.9, 11.0 ppm. For 3-methyl-1-(tetrahydropyran-2-yl)pyrazole, only the 3-*H*-pz (7.47 ppm, d, 1H, <sup>3</sup>J = 2.2 Hz) and 4-*H*-pz (6.06 ppm, d, 1H, <sup>3</sup>J = 2.2 Hz) protons could be clearly distinguished from the corresponding protons of the 5-methyl isomer in the <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of the isomer mixture obtained after heating the pure 5-methyl isomer to 125 °C in a pressure tube. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>NaO 189.1004; found 189.0998.

**4.3.2. 5-Ethyl-1-(tetrahydropyran-2-yl)pyrazole (3).** B.p. 90–91 °C (0.12 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>J = 1.5 Hz, 3-*H*-pz), 6.05 (d, 1H, <sup>3</sup>J = 1.5 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz, *CH*-THP), 4.00–4.05 (m, 1H, CH<sub>2</sub>O-THP), 3.60–3.66 (m, 1H, CH<sub>2</sub>O-THP), 2.62–2.78 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.44–2.54 (m, 1H, CH<sub>2</sub>-THP), 2.07–2.13 (m, 1H, CH<sub>2</sub>-THP), 1.91–1.98 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.77 (m, 3H, CH<sub>2</sub>-THP), 1.27 (t, 3H, <sup>3</sup>J = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 145.4, 139.1, 104.3, 84.3, 67.8, 29.5, 25.1, 23.0, 18.6, 12.8 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>NaO 203.1160; found 203.1158.

**4.3.3. 5-*n*-Propyl-1-(tetrahydropyran-2-yl)pyrazole (4).** B.p. 95–96 °C (0.20 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>J = 1.8 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>J = 1.6 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz, *CH*-THP), 4.00–4.06 (m, 1H, CH<sub>2</sub>O-THP), 3.60–3.67 (m, 1H, CH<sub>2</sub>O-THP), 2.56–2.71 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.44–2.55 (m, 1H, CH<sub>2</sub>-THP), 2.07–2.14 (m, 1H, CH<sub>2</sub>-THP), 1.90–1.97 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.77 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>-CH<sub>2</sub>CH<sub>3</sub>), 1.00 (t, 3H, <sup>3</sup>J = 7.3 Hz, (CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 143.8, 139.1, 105.0, 84.2, 67.8, 29.6, 27.3, 25.1, 23.0, 22.0, 14.0 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>NaO 217.1317; found 217.1298.

**4.3.4. 5-*n*-Butyl-1-(tetrahydropyran-2-yl)pyrazole (5).** B.p. 99–100 °C (0.10 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>J = 1.4 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>J = 1.8 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz, *CH*-THP), 4.00–4.06 (m, 1H, CH<sub>2</sub>O-THP), 3.60–3.67 (m, 1H, CH<sub>2</sub>O-THP), 2.59–2.72 (m, 2H, CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 2.44–2.55 (m, 1H, CH<sub>2</sub>-THP), 2.07–2.14 (m, 1H, CH<sub>2</sub>-THP), 1.90–1.97 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.77 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.41 (m, 2H, (CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.94 (t, 3H, <sup>3</sup>J = 7.3 Hz, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.0, 139.1, 104.9, 84.2, 67.8, 30.8, 29.6, 25.1, 25.0, 23.0, 22.5, 13.9 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>20</sub>N<sub>2</sub>NaO 231.1473; found 231.1474.

**4.3.5. 5-*n*-Pentyl-1-(tetrahydropyran-2-yl)pyrazole (6).** B.p. 104–106 °C (0.10 mmHg) (isomerization occurs). Before

distillation (after heating to 75 °C in vacuum, no isomerization): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>J = 1.5 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>J = 0.7 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz, *CH*-THP), 4.00–4.06 (m, 1H, CH<sub>2</sub>O-THP), 3.59–3.67 (m, 1H, CH<sub>2</sub>O-THP), 2.58–2.72 (m, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 2.44–2.55 (m, 1H, CH<sub>2</sub>-THP), 2.06–2.14 (m, 1H, CH<sub>2</sub>-THP), 1.90–1.97 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.78 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 1.31–1.41 (m, 4H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 0.90 (t, 3H, <sup>3</sup>J = 6.8 Hz, (CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.1, 139.1, 104.9, 84.2, 67.9, 31.6, 29.6, 28.3, 25.3, 25.1, 23.0, 22.5, 14.1 ppm. For 3-*n*-pentyl-1-(tetrahydropyran-2-yl)pyrazole, only the 3-*H*-pz (7.48 ppm, d, 1H, <sup>3</sup>J = 2.2 Hz), 4-*H*-pz (6.08 ppm, d, 1H, <sup>3</sup>J = 2.6 Hz) and *CH*-THP (5.30 ppm, dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz) protons could be clearly distinguished from the corresponding protons of the 5-*n*-pentyl isomer in the <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of the isomer mixture obtained after distillation. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>NaO 245.1630; found 245.1637.

**4.3.6. 5-*i*-Pentyl-1-(tetrahydropyran-2-yl)pyrazole (7).** B.p. 78–79 °C (~0.005 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>J = 1.5 Hz, 3-*H*-pz), 6.03 (d, 1H, <sup>3</sup>J = 0.7 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>J = 10.2 Hz, <sup>3</sup>J = 2.6 Hz, *CH*-THP), 4.03 (m, 1H, CH<sub>2</sub>O-THP), 3.63 (m, 1H, CH<sub>2</sub>O-THP), 2.66 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 2.50 (m, 1H, CH<sub>2</sub>-THP), 2.11 (m, 1H, CH<sub>2</sub>-THP), 1.94 (m, 1H, CH<sub>2</sub>-THP), 1.47–1.78 (m, 6H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.94 (d, 6H, <sup>3</sup>J = 6.6 Hz, (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.2, 139.2, 104.8, 84.2, 67.9, 37.7, 29.6, 27.8, 25.1, 23.2, 23.0, 22.5 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>NaO 245.1630; found 245.1609.

**4.3.7. 5-*n*-Hexyl-1-(tetrahydropyran-2-yl)pyrazole (8).** B.p. 121–123 °C (0.20 mmHg) (isomerization occurs). Before distillation: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>J = 1.3 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>J = 1.5 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz, *CH*-THP), 4.00–4.06 (m, 1H, CH<sub>2</sub>O-THP), 3.59–3.67 (m, 1H, CH<sub>2</sub>O-THP), 2.58–2.72 (m, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 2.44–2.55 (m, 1H, CH<sub>2</sub>-THP), 2.06–2.14 (m, 1H, CH<sub>2</sub>-THP), 1.90–1.97 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.78 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 1.26–1.42 (m, 6H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 0.89 (t, 3H, <sup>3</sup>J = 7.2 Hz, (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.1, 139.2, 104.9, 84.2, 67.9, 31.7, 29.6, 29.1, 28.6, 25.3, 25.1, 23.0, 22.7, 14.2 ppm. For the 3-*n*-hexyl-1-(tetrahydropyran-2-yl)pyrazole, only the 3-*H*-pz (7.48 ppm, d, 1H, <sup>3</sup>J = 2.2 Hz), 4-*H*-pz (6.08 ppm, d, 1H, <sup>3</sup>J = 2.2 Hz) and *CH*-THP (5.30 ppm, dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz) protons could be clearly distinguished from the corresponding protons of the 5-*n*-hexyl isomer in the <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of the isomer mixture obtained after distillation. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>24</sub>N<sub>2</sub>NaO 259.1786; found 259.1786.

**4.3.8. 5-*n*-Heptyl-1-(tetrahydropyran-2-yl)pyrazole (9).** B.p. 128–130 °C (0.15 mmHg) (isomerization occurs). Before distillation: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>J = 1.5 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>J = 1.5 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>J = 9.9 Hz, <sup>3</sup>J = 2.6 Hz, *CH*-THP), 4.03 (m, 1H, CH<sub>2</sub>O-THP), 3.63 (m, 1H, CH<sub>2</sub>O-THP), 2.58–2.72 (m, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 2.44–2.55 (m, 1H, CH<sub>2</sub>-THP), 2.06–2.14 (m, 1H, CH<sub>2</sub>-THP), 1.90–1.97 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.78 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 1.23–1.43 (m, 8H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 0.88 (t, 3H, <sup>3</sup>J = 6.8 Hz,

(CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.1, 139.1, 104.9, 84.2, 67.8, 31.8, 29.6, 29.4, 29.1, 28.7, 25.3, 25.1, 23.0, 22.7, 14.2 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>26</sub>N<sub>2</sub>NaO 273.1943; found 273.1924.

**4.3.9. 5-*n*-Octyl-1-(tetrahydropyran-2-yl)pyrazole (10).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>*J* = 1.7 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>*J* = 9.9 Hz, <sup>3</sup>*J* = 2.6 Hz, *CH*-THP), 4.03 (m, 1H, CH<sub>2</sub>O-THP), 3.63 (m, 1H, CH<sub>2</sub>O-THP), 2.65 (m, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>), 2.50 (m, 1H, CH<sub>2</sub>-THP), 2.11 (m, 1H, CH<sub>2</sub>-THP), 1.93 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.78 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 1.23–1.43 (m, 10H, (CH<sub>2</sub>)<sub>2</sub>-(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 6.8 Hz, (CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.1, 139.2, 104.9, 84.2, 67.9, 31.9, 29.6, 29.4 (two overlapping peaks), 29.3, 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>28</sub>N<sub>2</sub>NaO 287.2099; found 287.2084.

**4.3.10. 5-*n*-Nonyl-1-(tetrahydropyran-2-yl)pyrazole (11).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>*J* = 1.5 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>*J* = 9.9 Hz, <sup>3</sup>*J* = 2.6 Hz, *CH*-THP), 4.03 (m, 1H, CH<sub>2</sub>O-THP), 3.63 (m, 1H, CH<sub>2</sub>O-THP), 2.65 (m, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>), 2.50 (m, 1H, CH<sub>2</sub>-THP), 2.11 (m, 1H, CH<sub>2</sub>-THP), 1.93 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.78 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>), 1.20–1.42 (m, 12H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 6.8 Hz, (CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.1, 139.2, 104.9, 84.2, 67.9, 32.0, 29.8, 29.6, 29.47, 29.43, 29.39, 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>30</sub>N<sub>2</sub>NaO 301.2256; found 301.2247.

**4.3.11. 5-*n*-Decyl-1-(tetrahydropyran-2-yl)pyrazole (12).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>*J* = 1.5 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>*J* = 9.9 Hz, <sup>3</sup>*J* = 2.6 Hz, *CH*-THP), 4.03 (m, 1H, CH<sub>2</sub>O-THP), 3.63 (m, 1H, CH<sub>2</sub>O-THP), 2.65 (m, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>), 2.50 (m, 1H, CH<sub>2</sub>-THP), 2.11 (m, 1H, CH<sub>2</sub>-THP), 1.93 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.78 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>), 1.23–1.43 (m, 14H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 6.8 Hz, (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.1, 139.2, 104.9, 84.2, 67.9, 32.0, 29.68, 29.63, 29.59, 29.47, 29.43 (two overlapping peaks), 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>32</sub>N<sub>2</sub>NaO 315.2412; found 315.2412.

**4.3.12. 5-*n*-Dodecyl-1-(tetrahydropyran-2-yl)pyrazole (13).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (s, 1H, 3-*H*-pz), 6.04 (s, 1H, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>*J* = 9.9 Hz, <sup>3</sup>*J* = 2.6 Hz, *CH*-THP), 4.03 (m, 1H, CH<sub>2</sub>O-THP), 3.63 (m, 1H, CH<sub>2</sub>O-THP), 2.65 (m, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>), 2.50 (m, 1H, CH<sub>2</sub>-THP), 2.10 (m, 1H, CH<sub>2</sub>-THP), 1.93 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.78 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>), 1.23–1.43 (m, 18H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 6.6 Hz, (CH<sub>2</sub>)<sub>11</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.1, 139.2, 104.9, 84.2, 67.9, 32.0, 29.4–29.9 (eight overlapping peaks), 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>20</sub>H<sub>36</sub>N<sub>2</sub>NaO 343.2725; found 343.2724.

**4.3.13. 5-*n*-Hexadecyl-1-(tetrahydropyran-2-yl)pyrazole (14).** M.p. 54 °C. Purification of the 5-alkyl isomer was carried out by column chromatography. 15.5 g of crude material was loaded onto 800 g silica gel (Dynamic Adsorbents, 32–63 μ; stationary phase width/height: ~9.5 × 26 cm) and was eluted with ~6 L hexane/ethyl acetate (6 : 1). 3.8 g 1-iodohexadecane was

recovered as the first fraction, followed by 1.1 g of a mixture of 1-iodohexadecane and 1-(tetrahydropyran-2-yl)pyrazole, and finally by 9.4 g pure 5-*n*-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole. *R*<sub>f</sub> = 0.25 (TLC). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 1H, <sup>3</sup>*J* = 0.8 Hz, 3-*H*-pz), 6.04 (d, 1H, <sup>3</sup>*J* = 0.8 Hz, 4-*H*-pz), 5.24 (dd, 1H, <sup>3</sup>*J* = 10.1 Hz, <sup>3</sup>*J* = 2.4 Hz, *CH*-THP), 4.00–4.06 (m, 1H, CH<sub>2</sub>O-THP), 3.59–3.67 (m, 1H, CH<sub>2</sub>O-THP), 2.58–2.72 (m, 2H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>14</sub>CH<sub>3</sub>), 2.44–2.55 (m, 1H, CH<sub>2</sub>-THP), 2.07–2.14 (m, 1H, CH<sub>2</sub>-THP), 1.90–1.97 (m, 1H, CH<sub>2</sub>-THP), 1.54–1.78 (m, 5H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>13</sub>CH<sub>3</sub>), 1.18–1.42 (m, 26H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>13</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 6.8 Hz, (CH<sub>2</sub>)<sub>15</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 144.1, 139.1, 104.9, 84.2, 67.9, 32.0, 29.8 (seven overlapping peaks), 29.64, 29.59, 29.47 (two overlapping peaks), 29.43, 28.7, 25.3, 25.1, 23.0, 22.8, 14.2 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>24</sub>H<sub>44</sub>N<sub>2</sub>NaO 399.3351; found 399.3350.

**4.3.14. 1,6-Bis(1-(tetrahydropyran-2-yl)pyrazol-5-yl)hexane (15).** M.p. 70–71 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.45 (d, 2H, <sup>3</sup>*J* = 1.4 Hz, 3-*H*-pz), 6.03 (d, 2H, <sup>3</sup>*J* = 1.4 Hz, 4-*H*-pz), 5.23 (dd, 2H, <sup>3</sup>*J* = 9.9 Hz, <sup>3</sup>*J* = 2.6 Hz, *CH*-THP), 3.99–4.05 (m, 2H, CH<sub>2</sub>O-THP), 3.58–3.66 (m, 2H, CH<sub>2</sub>O-THP), 2.59–2.73 (m, 4H, CH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>2</sub>), 2.44–2.55 (m, 2H, CH<sub>2</sub>-THP), 2.06–2.14 (m, 2H, CH<sub>2</sub>-THP), 1.90–1.97 (m, 2H, CH<sub>2</sub>-THP), 1.54–1.77 (m, 10H, CH<sub>2</sub>-THP and CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.38–1.47 (m, 4H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 143.8, 139.1, 104.9, 84.2, 67.8, 29.6, 29.1, 28.5, 25.2, 25.1, 23.0 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>22</sub>H<sub>34</sub>N<sub>4</sub>NaO<sub>2</sub> 409.2579; found 409.2579.

#### 4.4. General procedure for the deprotection of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles (16–29)

5-Alkyl-1-(tetrahydropyran-2-yl)pyrazole (20 mmol) is dissolved in ethanol (200 mL) and conc. HCl (10 mL) is added dropwise under stirring. After stirring at room temperature for 8 hours, complete deprotection is indicated by the absence of 5-alkyl-1-(tetrahydropyran-2-yl)pyrazole signals in the <sup>1</sup>H NMR spectrum of the reaction mixture. The volatiles are removed on a Rotavap at 35 °C and the residual aqueous solution is neutralized with NaHCO<sub>3</sub> to pH ~8, followed by extraction with diethyl ether (3 × 100 mL) and drying of the combined organic layers with anhydrous MgSO<sub>4</sub>. After removing the solvent and drying under high vacuum, pure 5-alkylpyrazoles (by <sup>1</sup>H and <sup>13</sup>C NMR) are obtained, that can be further purified by vacuum distillation or recrystallization (solid products). In the case of 1,6-bis(1-(tetrahydropyran-2-yl)pyrazol-5-yl)hexane, neutralization with NaHCO<sub>3</sub> provides a white precipitate, which is filtered, washed with brine, dried, dissolved in hot nitrobenzene, filtered, and, after removal of the solvent, dried at 100 °C under high vacuum. The products are colorless oils, with the exception of the C<sub>16</sub> derivative and 1,6-bis(pyrazol-5-yl)hexane, which are colorless crystalline solids.

**4.4.1. 3(5)-Methylpyrazole (16).** B.p. 58–59 °C (0.16 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.48 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 3-*H*-pz), 6.07 (s, 1H, <sup>3</sup>*J* = 1.5 Hz, 4-*H*-pz), 2.34 (s, 3H, CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 143.2, 135.1, 104.5, 12.0 ppm.

**4.4.2. 3(5)-Ethylpyrazole (17).** B.p. 74–75 °C (0.70 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.50 (s, 1H, 3-*H*-pz), 6.09 (s, 1H, 4-*H*-pz), 2.72 (q, 2H, <sup>3</sup>*J* = 7.7 Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.28 (t, 3H, <sup>3</sup>*J* = 7.7 Hz, CH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 149.4, 135.1, 103.0, 20.1, 13.7 ppm.

**4.4.3. 3(5)-*n*-propylpyrazole (18).** B.p. 72–73 °C (0.12 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.49 (d, 1H, <sup>3</sup>*J* = 2.2 Hz, 3-*H*-pz), 6.08 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 4-*H*-pz), 2.65 (t, 2H, <sup>3</sup>*J* = 7.5 Hz, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.68 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.97 (t, 3H, <sup>3</sup>*J* = 7.3 Hz, (CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 147.7, 135.2, 103.6, 28.8, 22.8, 13.9 ppm.

**4.4.4. 3(5)-*n*-butylpyrazole (19).** B.p. 84–85 °C (0.10 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.48 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 3-*H*-pz), 6.08 (d, 1H, <sup>3</sup>*J* = 1.6 Hz, 4-*H*-pz), 2.67 (t, 2H, <sup>3</sup>*J* = 7.9 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 1.64 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.38 (m, 2H, (CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.93 (t, 3H, <sup>3</sup>*J* = 7.5 Hz, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 147.8, 135.2, 103.4, 31.7, 26.5, 22.5, 13.9 ppm.

**4.4.5. 3(5)-*n*-Pentylpyrazole (20).** B.p. 98–99 °C (0.11 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.49 (d, 1H, <sup>3</sup>*J* = 1.2 Hz, 3-*H*-pz), 6.08 (d, 1H, <sup>3</sup>*J* = 2.2 Hz, 4-*H*-pz), 2.66 (t, 2H, <sup>3</sup>*J* = 7.7 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 1.65 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 1.29–1.38 (m, 4H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 0.88 (m, 3H, (CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 148.2, 135.3, 103.5, 31.6, 29.2, 26.8, 22.5, 14.1 ppm.

**4.4.6. 3(5)-*i*-Pentylpyrazole (21).** B.p. 66 °C (~0.005 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.49 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 3-*H*-pz), 6.08 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 4-*H*-pz), 2.68 (t, 2H, <sup>3</sup>*J* = 7.9 Hz, CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 1.52–1.66 (m, 3H, CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 0.92 (d, 6H, <sup>3</sup>*J* = 6.6 Hz, (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 148.2, 135.2, 103.4, 38.5, 27.8, 24.7, 22.5 ppm. HRMS (ESI-TOF) *m/z*: [M – H]<sup>–</sup> calcd for C<sub>8</sub>H<sub>13</sub>N<sub>2</sub> 137.1079; found 137.1084.

**4.4.7. 3(5)-*n*-Hexylpyrazole (22).** B.p. 126–127 °C (0.20 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.48 (d, 1H, <sup>3</sup>*J* = 1.5 Hz, 3-*H*-pz), 6.08 (d, 1H, <sup>3</sup>*J* = 1.5 Hz, 4-*H*-pz), 2.66 (t, 2H, <sup>3</sup>*J* = 7.9 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 1.65 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 1.26–1.40 (m, 6H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 0.88 (t, 3H, <sup>3</sup>*J* = 7.0 Hz, (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 148.1, 135.5, 103.5, 31.7, 29.5, 29.1, 26.8, 22.7, 14.2 ppm.

**4.4.8. 3(5)-*n*-Heptylpyrazole (23).** B.p. 112–119 °C (0.10 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.48 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 3-*H*-pz), 6.08 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 4-*H*-pz), 2.66 (t, 2H, <sup>3</sup>*J* = 7.7 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 1.65 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 1.20–1.39 (m, 8H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 7.0 Hz, (CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 148.0, 135.6, 103.4, 31.9, 29.5, 29.4, 29.2, 26.8, 22.7, 14.2 ppm.

**4.4.9. 3(5)-*n*-Octylpyrazole (24).** B.p. 126–128 °C (0.15 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.48 (d, 1H, <sup>3</sup>*J* = 2.0 Hz, 3-*H*-pz), 6.08 (d, 1H, <sup>3</sup>*J* = 2.0 Hz, 4-*H*-pz), 2.66 (t, 2H, <sup>3</sup>*J* = 7.7 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>), 1.64 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 1.20–1.40 (m, 10H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 7.0 Hz, (CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 148.0, 135.3, 103.4, 32.0, 29.54, 29.47, 29.43, 29.3, 26.8, 22.8, 14.2 ppm.

**4.4.10. 3(5)-*n*-Nonylpyrazole (25).** B.p. 140–142 °C (0.07 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.48 (d, 1H, <sup>3</sup>*J* = 1.8 Hz,

3-*H*-pz), 6.08 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 4-*H*-pz), 2.66 (t, 2H, <sup>3</sup>*J* = 7.9 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>), 1.65 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>), 1.20–1.40 (m, 12H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 7.0 Hz, (CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 148.1, 135.3, 103.4, 32.0, 29.6, 29.53, 29.50, 29.42, 29.40, 26.8, 22.8, 14.2 ppm.

**4.4.11. 3(5)-*n*-decylpyrazole (26).** B.p. 131 °C (~0.005 mmHg). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.48 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 3-*H*-pz), 6.08 (s, 1H, <sup>3</sup>*J* = 1.8 Hz, 4-*H*-pz), 2.65 (t, 2H, <sup>3</sup>*J* = 7.7 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>), 1.64 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>), 1.23–1.37 (m, 14H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 6.8 Hz, (CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 148.1, 135.4, 103.5, 32.0, 29.69, 29.65, 29.5 (two overlapping peaks), 29.4 (two overlapping peaks), 26.8, 22.8, 14.2 ppm.

**4.4.12. 3(5)-*n*-Dodecylpyrazole (27).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.49 (d, 1H, <sup>3</sup>*J* = 1.8 Hz, 3-*H*-pz), 6.07 (s, 1H, <sup>3</sup>*J* = 1.5 Hz, 4-*H*-pz), 2.68 (t, 2H, <sup>3</sup>*J* = 7.9 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>), 1.66 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>), 1.18–1.38 (m, 18H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>13</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 6.8 Hz, (CH<sub>2</sub>)<sub>11</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 147.9, 135.2, 103.6, 32.0, 29.7–29.8 (three overlapping peaks), 29.6, 29.4–29.5 (four overlapping peaks), 26.8, 22.8, 14.2 ppm.

**4.4.13. 3(5)-*n*-Hexadecylpyrazole (28).** M.p. 46.5–47 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.48 (s, 1H, 3-*H*-pz), 6.08 (s, 1H, 4-*H*-pz), 2.65 (t, 2H, <sup>3</sup>*J* = 7.7 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>14</sub>CH<sub>3</sub>), 1.64 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>13</sub>CH<sub>3</sub>), 1.18–1.38 (m, 26H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>), 0.87 (t, 3H, <sup>3</sup>*J* = 6.8 Hz, (CH<sub>2</sub>)<sub>15</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): 148.0, 135.3, 103.5, 32.0, 29.4–30.0 (twelve overlapping peaks), 26.8, 22.8, 14.2 ppm. HRMS (ESI-TOF) *m/z*: [M – H]<sup>–</sup> calcd for C<sub>19</sub>H<sub>35</sub>N<sub>2</sub> 291.2800; found 291.2780.

**4.4.14. 1,6-Bis(pyrazol-3(5)-yl)hexane (29).** M.p. 87–88 °C (for the hydrate: m.p. 68–69 °C). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): 7.46 (s, 2H, 3-*H*-pz), 6.02 (s, 2H, 4-*H*-pz), 2.55 (t, 4H, <sup>3</sup>*J* = 7.7 Hz, CH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>2</sub>), 1.56 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.30 (m, 4H, (CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>): 147.2, 134.8, 103.4, 29.5, 29.0, 26.5 ppm. HRMS (ESI-TOF) *m/z*: [M – H]<sup>–</sup> calcd for C<sub>12</sub>H<sub>17</sub>N<sub>4</sub> 217.1453; found 217.1470.

## 4.5. One-pot synthesis

(a) Pyrazole (10.000 g, 0.1469 mol) and 3,4-dihydro-2*H*-pyran (16.75 mL, 15.44 g, 0.1836 mol) are added to a 500 mL round-bottom pressure flask, which is sealed with a PTFE front seal bushing. The pyrazole dissolves completely in the 3,4-dihydro-2*H*-pyran and provides a homogeneous solution. The flask is placed in an oven and kept at 125 °C for 24 hours. After cooling to room temperature, the excess unreacted 3,4-dihydro-2*H*-pyran is removed under vacuum. (b) The flask containing pure 1-(tetrahydropyran-2-yl)pyrazole is evacuated and purged with N<sub>2</sub>. Anhydrous THF (300 mL) is added *via* N<sub>2</sub> purged syringe, and the solution is chilled to –78 °C under stirring for 30 minutes. <sup>n</sup>BuLi (1.6 M in hexanes, 92 mL, 0.15 mol) is added drop-wise over 90 minutes. After stirring for an additional 30 minutes at –78 °C, 1-haloalkane (Method A: 0.1616 mol; Method B: 0.1335 mol) is added *via* syringe. The solution is stirred at –78 °C for 3 hours, then is left to warm up to room temperature overnight. The THF solvent and the excess haloalkane (Method A) or excess 1-THP-pyrazole (Method B) are

removed under vacuum. (c) Deprotection is accomplished by dissolving the 5-alkyl-1-(tetrahydropyran-2-yl)pyrazoles in EtOH (300 mL) and stirring with 37% HCl (50 mL) for 4 hours. The solvent is removed under vacuum at 35 °C, the residue is neutralized with saturated aqueous NaHCO<sub>3</sub> solution (to pH ~8) and is extracted with diethyl ether (5 × 100 mL). The combined organic fractions are washed with brine (100 mL) and dried over anhydrous MgSO<sub>4</sub>. If 1-iodoalkane was used in the second step, additional washing with a dilute aqueous sodium thiosulfate solution is employed before drying with MgSO<sub>4</sub>, to remove iodine contamination. After filtration and evaporation of the solvent, the product is dried in vacuum (for longer alkyl chains the drying is carried out at 75 °C, to remove any remaining traces of haloalkane). Pure 3(5)-alkylpyrazoles (by <sup>1</sup>H-NMR) are thus obtained, which can be further purified by vacuum distillation. For 3(5)-hexylpyrazole (obtained by Method A from 1-bromohexane), yield: 20.536 g (92%). For 3(5)-decylpyrazole (obtained by Method B from 1-bromodecane), yield: 27.675 g (91%).

#### 4.6. X-ray crystallography

Crystals of 1,6-bis(pyrazol-3(5)-yl)hexane hydrate were grown by slow cooling of a hot aqueous solution to which a small amount of methanol was added. Crystals of 5-*n*-hexadecyl-1-(tetrahydropyran-2-yl)pyrazole were grown by slow evaporation of a methanolic solution containing a small amount of water. X-ray diffraction data were collected at room temperature from a single-crystal mounted atop a glass fiber with cyanoacrylate glue, with a Bruker SMART APEX II diffractometer using graphite-monochromated Mo-K $\alpha$  ( $\lambda = 0.71073$  Å) radiation. The structures were solved by employing SHELXT intrinsic phasing methods and refined by full-matrix least squares on  $F^2$ , using the APEX2 v2014.9-0 software package.<sup>34</sup> All non-H atoms were refined with independent anisotropic displacement parameters. Hydrogen atoms were placed at calculated positions and refined using a riding model, except for the water hydrogens, which were located from the Fourier difference density maps and refined using a riding model with O–H distance restraints.<sup>†</sup> Crystallographic details are summarized in Table 3.

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