EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000674

Link to VoR: https://doi.org/10.1002/ejoc.202000674

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Primary Vinyl Ethers as Acetylene Surrogate: a Flexible Tool for Deuterium-Labeled Pyrazole Synthesis

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Abstract: A novel synthetic path to 1,3-disubstituted pyrazoles and their deuterated derivatives was developed. It is based on the reaction of vinyl ethers with hydrazonoyl chlorides in the presence of triethylamine. The reaction mechanism, clarified by the joint experimental and computational study, involves 1,3-dipolar cycloaddition of the *in situ* generated nitrile imines to vinyl ethers and subsequent cleavage of alcohol from the formed alkoxypyrazoline. The results highlight the possibility of using vinyl ethers as acetylene surrogate and provide a novel access to pyrazoles, 4,5-dideuteropyrazoles and their regioselectively labeled derivatives, 5-deuteropyrazoles.

Introduction

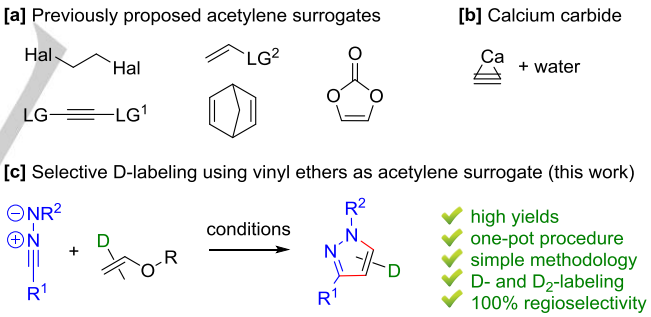
With the triple bond prone to additions and two active C-bonded protons, acetylene is invaluable for a variety of transformations.[1] However, its synthetic potential cannot be fully implemented because bulk gaseous acetylene is flammable and explosive.[1a, 1c] Safer replacements for acetylene have been proposed, including dihaloethanes,[2] vinylene carbonate,[3] mono-functionalized ethylenes,[4] substituted alkynes with a potent leaving group,[5] and some other molecules.[6] Application of some of these acetylene surrogates may imply an additional step (to get rid of the leaving group) or/and involve the use of specific reagents for activation (Scheme 1, [a]).[2-6]

Among the acetylene surrogates, calcium carbide represents a highly efficient and convenient acetylene source. It reacts with water to produce acetylene. This procedure can be safely performed on any scale and is perfect for the *in situ* acetylene generation in laboratory settings.[7] It provides a convenient access to pyrazoles and 4,5-dideuteropyrazoles (when using D_2O instead of water, Scheme 1, [b]).[8] Despite its convenience, deuteration with CaC_2 is of limited scope and requires application of aprotic or deuterated solvents to achieve high levels of deuterium incorporation.[8-9]

The importance of deuterated substances in chemistry,[10] medical biology[11] and physics[12] is undeniable.[13] D-labeled compounds allow studying reaction mechanisms[14] and altering reaction selectivities[15] in total syntheses of complex pharmaceuticals. They are extensively used in pharmacokinetic studies.[11, 16] The first deuterated drug, deutetrabenazine, has been recently approved by FDA.[17] This milestone reflects the growing demand for deuterium-labeled compounds and the interest in new methods for isotope labeling.

Studying vinyl ethers, we stumbled across an interesting opportunity of applying them as acetylene surrogates. The idea was tested in a synthesis of non-labeled, dideuterated and regioselectively labeled 5-deuteropyrazoles (Scheme 1, [c]). In this study, for the first time was proposed a detailed mechanistic investigation of the reaction between vinyl ethers and *in situ* generated nitrile imines, resulting into the novel synthetic approach to 1,3-disubstituted pyrazoles and their mono- and dideuterated derivatives.

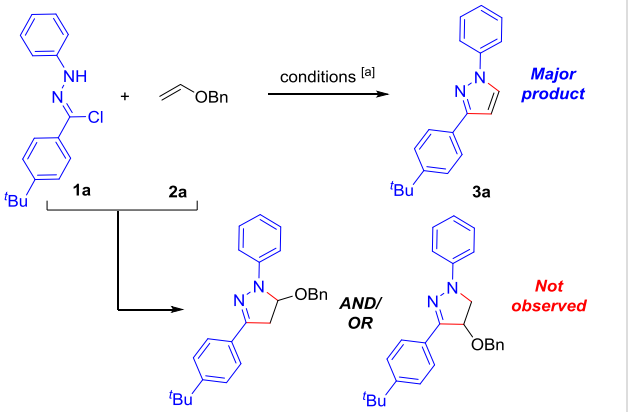
Scheme 1. Acetylene surrogates in chemical processes.



Results and Discussion

A preliminary ^{1}H NMR investigation of the reaction mixtures with a variety of nitrile imine sources, hydrazonoyl chlorides, and vinyl ethers in the presence of base demonstrated the possibility for their direct transformation to pyrazoles, but not pyrazolines, as we could expect (as depicted in Table 1). This transformation seemed very promising, so we decided to investigate it in detail. The readily available *tert*-butyl substituted hydrazonoyl chloride **1a** was reacted with benzyl vinyl ether **2a** in different solvents (Table 1, Entries 1-14) and the best results were observed in benzene (Table 1, Entries 8,9). After varying concentration of **2a** (Table 1, Entries 6, 9-11) and reaction time (Table 1, Entries 9, 14), the best conditions were founded. The spectral yield of **3a** reached 93% at 80 °C starting from 70 mg/ml concentration of **2a** (Table 1, Entry 9).

Table 1. Optimization of the reaction conditions.

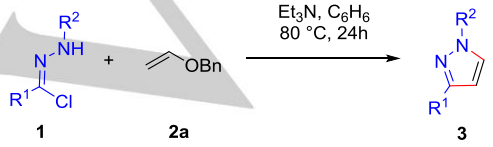


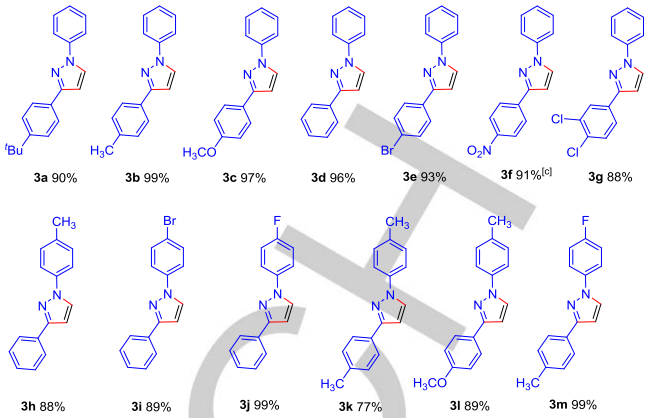
Entry	Solvent	Concentration of **2a**, mg/ml	T, ° C	Time, h	Yield of **3a**, %[b]
1	CH_2Cl_2	20	35	96	7
2	$CHCl_3$	20	35	96	10
3	$CHCl_3$	20	50	96	13
4	CH_3CN	20	50	96	47
5	toluene	20	50	96	45
6	benzene	20	50	96	47
7	$CHCl_3$	70	50	96	63
8	benzene	70	50	96	75
9	benzene	70	80	24	93 (90)
10	benzene	50	80	24	83
11	benzene	100	80	24	86
12	CH_3CN	70	80	24	71
13	toluene	70	80	24	70
14	benzene	70	80	12	77

[a] Reaction conditions: **1a** (1.5 equiv), **2a** (6-30 µl, 0.045-0.225 mmol), solvent (300 µl), triethylamine (1.5 equiv), temperature, time. [b] Spectral yields are given; the isolated yield for Entry 9 is shown in parentheses.

With the optimized conditions in hand, we tested a scope of hydrazonoyl chlorides **1a-m** to obtain the corresponding pyrazoles **3a-m** (see Table 2 for the details). Among them, 3-(4-*tert*-butyl)phenyl-, 3-(4-tolyl)-, 3-(4-methoxyphenyl)- and 3-(4-bromophenyl)-substituted *N*-phenylpyrazoles **3a-c** and **3e** were obtained in 90-99% isolated yields, and 1,3-diphenylpyrazole **3d** was obtained in 96% yield. To achieve full conversion of benzyl vinyl ether **2a** in the reaction with nitro-substituted hydrazonoyl chloride **1f**, the reaction time was increased to 48 h to afford the desired pyrazole **2f** in 91% yield. The yield of 3-(3,4-dichlorophenyl)- derivative **3g** was high, 88%. *N*-(4-Tolyl)- and *N*-(4-bromophenyl)-functionalized pyrazoles **3h** and **3i** were obtained in 88% and 89% yields, respectively. The yields of *N*-(4-fluorophenyl) derivatives **3j** and **3m** were nearly quantitative. 1,3-Di(4-tolyl)pyrazole **3k** and 3-(4-methoxyphenyl)-1-(4-tolyl)pyrazole **3l** were obtained in good yields (77% and 89%, respectively).

Table 2. A scope of products for the transformation with benzyl vinyl ether.[a,b]

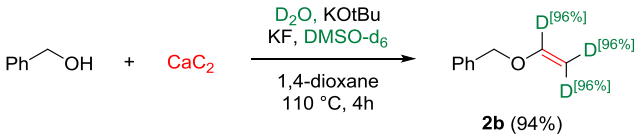




[a] Reaction conditions: **1a-m** (1.5 mmol), **2a** (1.0 mmol), benzene (2.0 ml), triethylamine (1.5 mmol), 80 °C, 24 h. [b] Isolated yields are given. [c] The reaction time was 48 h.

We have previously proposed a methodology for the synthesis of D_3-vinyl ethers from the mixture of alcohol, calcium carbide and D_2O.[18] To its certain disadvantage, the procedure depends on the use of DMSO-d_6 as a solvent and a substrate for the D_3-vinyl group formation. Besides, DMSO-d_6 has been shown to participate in side H-D exchange processes with active protons e.g. the CH_2 protons in benzyl alcohol.[18] As vinylations can be also carried out in 1,4-dioxane[19] which do not enter in any role to the hydrogen exchange processes,[20] we attempted to use 1,4-dioxane as a solvent instead of DMSO to avoid the undesirable H-D exchange and make the procedure more economic. We modified the procedure by diluting a small amount of DMSO-d_6 with 1,4-dioxane. The modified procedure afforded benzyl D_3-vinyl ether **2b** in 94% yield with 96% isotopic purity (Scheme 2, see Supporting Information for details). No side exchange processes involving the CH_2 protons in benzyl group were observed during the procedure.

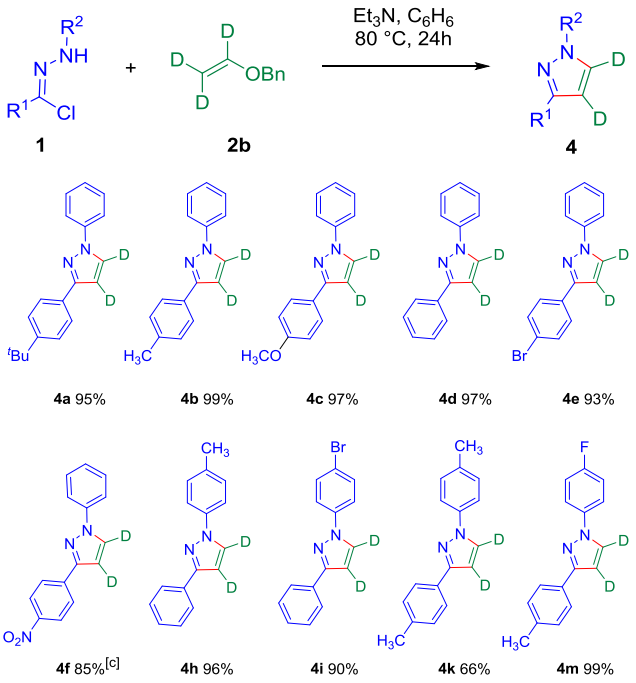
Scheme 2. Synthesis of benzyl D_3-vinyl ether **2b**.



Reaction conditions: CaC_2 (2.0 mmol), benzyl alcohol (0.7 mmol), KO^{t}Bu (0.7 mmol), KF (0.9 mmol), DMSO-d_6 (120 µl), D_2O (4.0 mmol), 1,4-dioxane (1.0 ml), 110 °C, 4 h.

Benzyl D_3-vinyl ether **2b** (synthesized from the readily available benzyl alcohol, calcium carbide and D_2O by the upgraded D_3-vinylation procedure) was reacted with various hydrazonoyl chlorides to afford 4,5-dideuteropyrazoles **4a-m** (Table 3). Among them, the donor-substituted 4,5-D_2-pyrazoles **4a-c**, 4,5-dideutero-1,3-diphenylpyrazole **4d**, and a bromo-derivative **4e** were obtained in 93-99% isolated yields. The yield of nitro-substituted dideuteropyrazole **4f** was good, 85%. 4,5-D_2-pyrazoles **4h** and **4i** were obtained in 96% and 90% yields, respectively. The yield of 4,5-dideutero-1,3-di(4-tolyl)pyrazole **4k** was moderate (66%), whereas **4m** was obtained in nearly quantitative yield.

Table 3. A scope for the transformation of benzyl D_3-vinyl ether **2b**.[a,b]

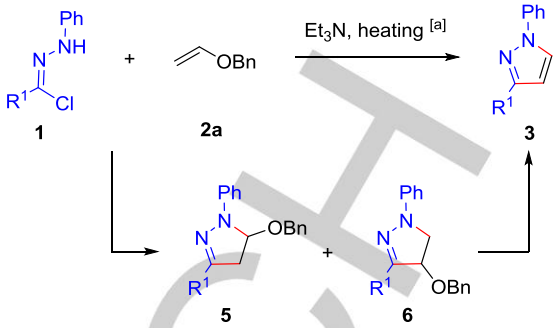


[a] Reaction conditions: **1a-m** (1.5 mmol), **2b** (1.0 mmol), benzene (2.0 ml), triethylamine (1.5 mmol), 80 °C, 24 h. [b] Isolated yields are given; deuterium incorporation corresponds to the level observed for **2b** (96%). [c] The reaction time was 48 h.

Further, the study of the reaction mechanism was performed. For this purpose, reaction mixtures with six selected hydrazonoyl chlorides **1a-f** and benzyl vinyl ether **2a** were investigated by ^{1}H NMR at various conditions (Table 4). In some cases, pyrazoline intermediate was revealed and it was invariably detected as a single regioisomer **5**. The alternative regioisomer **6** was not observed. The reactions with alkylphenyl-substituted hydrazonoyl chlorides **1a** and **1b** were too fast to allow "catching" the intermediate, with only the starting vinyl ether **2a** and the final aromatic products **3a,b** observed in the reaction mixture (Table 4, Entries 1-5). The use of 4-methoxyphenyl- or phenyl-substituted substrates allowed observation of intermediates, respectively, **5c** and **5d** by ^{1}H NMR at room temperature (Table 4, Entry 6,9). At elevated temperatures these intermediates were not detected in the reaction mixtures (Table 4, Entries 6-11).

The use of substrates **1e** and **1f** with 4-bromo- and 4-nitrophenyl substituents allowed detection of corresponding intermediates **5** even under heating (Table 4, Entries 12-20). ^{1}H NMR signals for the CH(OBn) group in **5e** and **5f** were observed at 5.95 ppm (dd, J = 8.7, 2.3 Hz) and 6.04 ppm (dd, J = 8.7, 2.3 Hz), respectively. ^{1}H NMR signals for pyrazoline CH_2-group proton in **5e** and **5f** were observed at 3.24 ppm (dd, J = 18.3, 2.3 Hz) and 3.30 ppm (dd, J = 18.5, 2.3 Hz), respectively; the signals for the second proton of CH_2 group partially overlapped with the standard. The mixture with 4-nitrophenyl derivative **1f** was additionally examined by HRMS-ESI, and a peak corresponding to the intermediate **5f** was clearly detected ($C_{22}H_{19}N_3O_3Na^+$, m/z 396.1304).

Table 4. NMR study of the reaction mixtures.

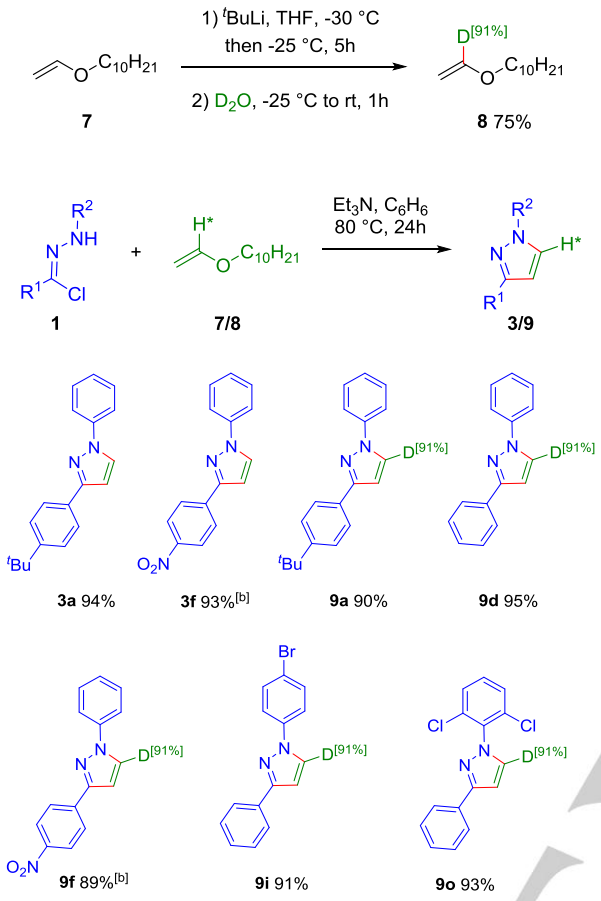


Entry	Substrate (R^1)	T, °C	Time, h	Ratio[b]			
				2a	**5**	**6**	**3**
1	**1a** (4-^{t}BuC$_6$H$_4$)	40	24	68	0	ND	32
2	**1a**	80[c]	24	3	0	ND	97
3	**1b** (4-MeC$_6$H$_4$)	20	120	15	0	ND	85
4	**1b**	40	24	0	0	ND	100
5	**1b**	80[c]	24	0	0	ND	100
6	**1c** (4-MeOC$_6$H$_4$)	20	120	17	42	ND	41
7	**1c**	40	24	4	0	ND	96
8	**1c**	80[c]	24	0	0	ND	100
9	**1d** (Ph)	20	120	16	68	ND	16
10	**1d**	40	24	5	0	ND	95
11	**1d**	80[c]	24	0	0	ND	100
12	**1e** (4-BrC$_6$H$_4$)	20	120	28	61	ND	11
13	**1e**	40	24	23	15	ND	62
14	**1e**	40	48	22	1	ND	77
15	**1e**	40	120	21	<1	ND	79
16	**1e**	80[c]	24	0	0	ND	100
17	**1f** (4-NO$_2$C$_6$H$_4$)	50	72	22	56	ND	22
18	**1f**	50[c]	72	10	81	ND	9
19	**1f**	80[c]	24	9	13	ND	78
20	**1f**	80[c]	48	7	0	ND	93

[a] Reaction conditions: **1a-f** (0.224 mmol), **2a** (0.15 mmol), $CHCl_3$ (300 µl), triethylamine (0.224 mmol), time, temperature. [b] Molar percents for the components are given. [c] The reactions were carried out in benzene.

With the results of NMR investigation in our hands, we performed a series of regioselective D-labeling experiments. Decyl 1-deuterovinyl ether **8** was synthesized by consequent lithiation of decyl vinyl ether **7** and treatment of the resulting organolithium compound by D_2O (Scheme 3, upper line). At first, the reaction of decyl vinyl ether **7** with hydrazonoyl chlorides was investigated. The reactivity of decyl vinyl ether **7** under optimized conditions was exceptionally good: *tert*-butyl- and nitrophenyl-substituted substrates **1a** and **1f** were transformed into pyrazoles **3a** and **3f** in 94 and 93% yields, respectively (Scheme 3). After that, decyl 1-deuterovinyl ether **8** was applied in cycloaddition reactions under optimized conditions, giving 5-deuteropyrazoles **9** in up to 95% yields with 100% regioselectivity (Scheme 3). Thus, the proposed methodology turned out to be highly suitable for the regioselective synthesis of 5-deuterated pyrazoles in mild conditions.

Scheme 3. Application of decyl vinyl ether **7** and its D-labeled derivative **8** for the synthesis of pyrazoles **3** and 5-deuteropyrazoles **9**.[a]



[a] Reaction conditions are specified in Tables 2,3; isolated yields are given in the scheme. [b] The reaction time was 48 h.

We obtained independent evidence for the prevalence of **1⟶5⟶3** path by performing quantum chemical modeling of the underlying cycloaddition process. Two possible paths are shown in Scheme 4. The modeled process starts with formation of two alternative pre-addition intermediates (**10'** or **10''** at Scheme 4).

On a qualitative level, cycloaddition regioselectivity can be explained by the consideration of Lewis' structures of **10'** and **10''**. In **10'** and, as well as in **TS1**, the negatively charged N atom interacts with the electron-deficient carbon atom adjacent to the withdrawing substituent -OBn. Analysis of Mulliken charges in **10'** and **10''** corroborates this qualitative prediction, see Figure 1. For simplicity, we computed Mulliken charges at the ZINDO/S//GFN2-xTB level of theory for the case of R = H. Clearly, electrostatic interaction in **10'** facilitates the formation of the transition state **TS1**.

Concerted dipolar cycloaddition proceeds via a five-membered ring transition state (**TS1** or **TS2** at Scheme 4). The reaction product is formed by elimination of benzyl alcohol at the final stage (**5⟶3** or **6⟶3**). We compared thermodynamics and kinetics of **10⟶5** and **10⟶6**. Calculated Gibbs free energies of the benzyl vinyl ether addition to nitrile imine **10** (a dehydrohalogenated derivative of **1**) in benzene (with solvation accounted for by SMD) are given in Table 5. Formation of the pre-addition intermediate (**10'** or **10''**) is endergonic, as estimated at the ωB97X-V/def2-TZVP-gCP//GFN2-xTB level. Apparently, the loss in translational entropy upon its formation is greater than the gain in enthalpy upon its binding to **2a**. Due to the relative instability of **10'** or **10''**, we estimated **10⟶TS1** and **10⟶TS2** as the activation free energy of cycloaddition.

Scheme 4. Model paths for the transformation of *in situ* generated nitrile imine to pyrazole (**1⟶3**); see Figures 1 and S37 as an example of optimized structures.

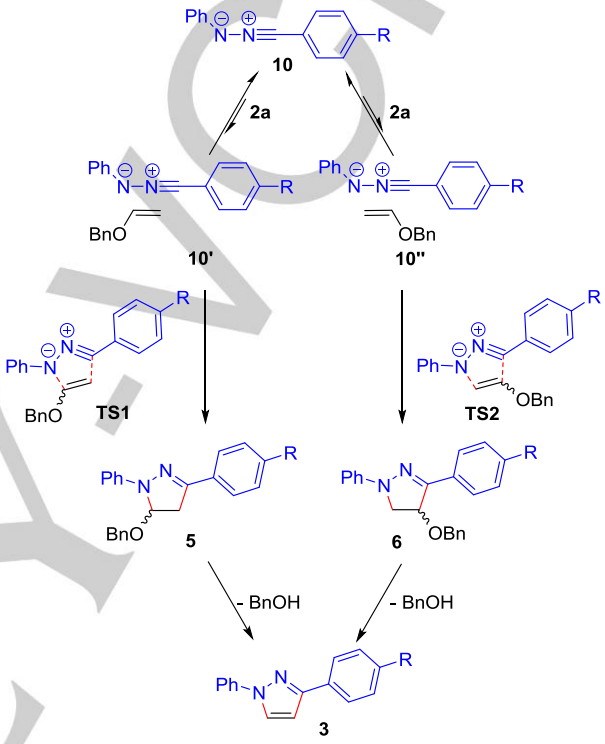


Figure 1. Optimized geometries at the GFN2-xTB level of the pre-cycloaddition intermediates **10'** and **10''** and Mulliken charges (in a.u) at the ZINDO/S//GFN2-xTB level (dotted lines connect the bonding atoms.).

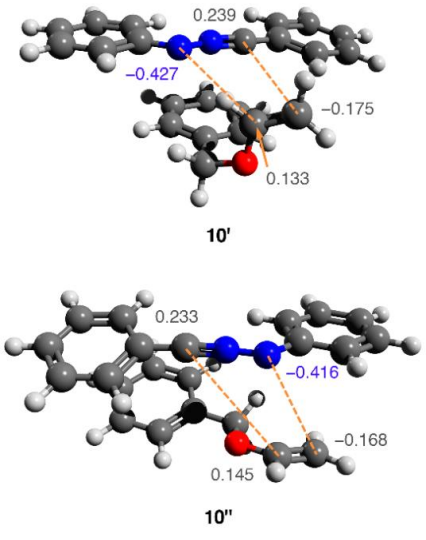


Table 5. Free energies (kcal/mol) calculated for the transformations shown in Scheme 4, as modeled at the ωB97X-V/def2-TZVP-gCP//GFN2-xTB level with SMD for benzene (see Supporting Information for the results of B97-3c-based modeling).

Entry	R[a]	10⟶10'	10'⟶5	10⟶TS1	5⟶3	10⟶10''	10''⟶6	10⟶TS2	6⟶3	$\Delta\Delta G_{rxn}$[b]	$\Delta\Delta G^{\neq}$[c]
1	Br	5.8	-64.0	22.8	-18.6	8.0	-61.7	28.0	-23.2	0.1	5.2
2	H	6.3	-63.2	22.3	-18.7	7.3	-59.9	29.0	-23.0	2.4	6.6
3	Me	6.2	-62.7	23.8	-18.5	7.6	-59.6	28.7	-23.0	1.8	4.8
4	NO_2	6.3	-65.1	21.3	-19.3	6.1	-61.0	27.1	-23.4	4.3	5.8
5	OMe	6.1	-62.8	23.8	-18.2	7.1	-59.1	28.4	-23.0	2.6	4.6

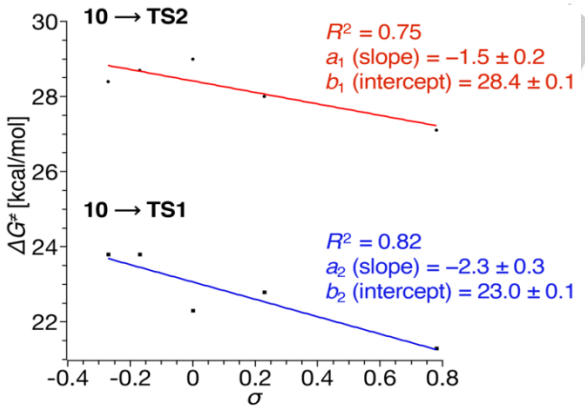
[a] The *para*-substituent, see Scheme 4; [b] $\Delta\Delta G_{rxn}$ is the difference between $\Delta G_{10\rightarrow6}$ and $\Delta G_{10\rightarrow5}$; [c] $\Delta\Delta G^{\neq}$ is the difference between $\Delta G_{10\rightarrow TS2}$ and $\Delta G_{10\rightarrow TS1}$.

The calculated activation free energies of cycloaddition ranged from 21.3 to 23.8 kcal/mol for **TS1** and from 27.1 to 28.4 kcal/mol for **TS2** (Table 5). More detailed structural information is given in Supporting Information. The left path in Scheme 4 proceeds over a barrier below 24 kcal/mol, which allows cycloaddition at room temperature within hours.[21] By contrast, the right path in Scheme 4 at ambient conditions is kinetically forbidden.

In all modeled cases, cycloaddition was highly exergonic. Formation of intermediate **5** was thermodynamically preferred over formation of **6** in all cases except R = Br. Both kinetic and thermodynamic favorability of **5** is consistent with the lack of detectable **6** in the experimental mixtures. At the same time, the strong preference for **5** explains the perfect regioselectivity of deuteration (Scheme 3).

As shown by Hammett equation-based analysis, nature of the substituent moderately affects the cycloaddition kinetics (Figure 2). Slopes of the Hammett plots for **10⟶TS1** and **10⟶TS2** are -2.3 and -1.5 kcal/mol per σ unit, respectively, which is flat, considering that the corresponding intercepts are 23.0 and 28.4 kcal/mol. For the favored path **1⟶5⟶3** via **TS1**, the effect is more pronounced, which indicates more facile formation of **5** for the substrates with electron-withdrawing substituents, e.g. R = NO_2, compared to the substrates with donating substituents.

Figure 2. Effect of the substituent on the activation free energy of cycloaddition. Least squares regression lines are given in red and blue. Hammett parameters were adopted from [22].



The final stage, dehydrobenzylation, is highly exergonic irrespective of the *para*-substituent R and the path, **5⟶3** or **6⟶3** (Table 5). At the same time, we saw that with the electron-withdrawing NO_2-group in **1f**, intermediate **5** accumulated in the system and persisted even at an elevated temperature of 80 °C. A similar effect, though less pronounced, was observed for **1e**. We could not locate neither E1 nor E2 transition states of dehydrobenzylation by using the implicit solvent approach at the selected level of theory. The existence of both E1 and E2 should not be excluded in further studies. For now, we will accept a *post hoc* explanation corroborated by experimental evidence and given below.

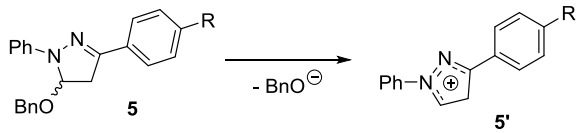
The increased kinetic stability of **5** with electron-withdrawing *para*-substituents is consistent with the E1 elimination mechanism, if we assume the validity of the Brønsted–Evans–Polanyi principle to estimate the activation energy E_a for this stage:

$E_a \propto \Delta H_{5\rightarrow5'}$,

Table 6 shows that relative enthalpy of the endothermic BnO^- dissociation $\Delta H_{5\rightarrow5'}$ becomes more pronounced as the electron-withdrawing effect of R increases. The electron-withdrawing NO_2- and Br-substituents destabilize the conjugated cation **5'** and therefore may hamper the **5⟶3** transition.

Some extra single-point energy evaluations were performed to independently estimate kinetics and thermodynamics of the elementary reactions depicted in Scheme 4. Switching computational method to B97-3c//GFN2-xTB significantly reduced the exergonic effects of **1'⟶5** and **1''⟶6** cycloadditions by +17.0 kcal/mol on average (depending on the substituent R, see Supporting Information). A concomitant average decrease in the free energy of activation for cycloaddition stage was -6.4 kcal/mol. The B97-3c is a computationally cheap yet accurate method, according to benchmarks;[23] nevertheless, calculations with the ωB97X-V functional can be significantly more accurate for the prediction of cycloaddition thermodynamics.[24] It should also be noted, that both levels of theory give, qualitatively, the same results. Therefore, the computations at the B97-3c//GFN2-xTB level, presented in Supporting Information, generally confirm the proposed mechanism.

Table 6. Dissociation of BnO^- from **5** and the corresponding reaction enthalpies.



Entry	R	$\Delta H_{5\rightarrow5'}$ [a]	σ [b]
1	Br	4.0	0.23
2	H	1.9	0.0
3	Me	0.9	−0.17
4	NO_2	6.6	0.78
5	OMe	0	−0.27

[a] Calculated at the ωB97X-V/def2-TZVP-gCP//GFN2-xTB level. [b] The Hammett σ values were adopted from ref. [22]

To summarize, transformation **10⟶3**, as a whole, is a thermodynamically favorable and kinetically feasible process that takes **10⟶5⟶3** pathway. Accordingly, excellent yields have been obtained in almost all cases under elevated temperatures (Tables 2,3 and Scheme 3). The nature of *para*-substituent R in **1** has opposite effects on the kinetics of cycloaddition and dehydrobenzylation stages.

Conclusion

The article provides detailed analysis of the reaction between vinyl ethers and *in situ* generated nitrile imines. The interaction leads to 5-alkoxydihydropyrazoles, which are rapidly converted to pyrazoles. A reaction mechanism was confirmed by NMR study and computational study, which demonstrated the excellent regioselectivity of the first step, [3+2] cycloaddition reaction leading to the formation of intermediate, 5-alkoxydihydropyrazole.

The mechanistic investigation resulted in the development of the novel access to 1,3-disubstituted pyrazoles, 4,5-dideuteropyrazoles and regioselectively labeled 5-deuteropyrazoles. The application of only 1 equivalent of deuterated substrate and no necessity in deuterated solvent for the synthesis of D-labeled pyrazoles means high cost efficiency of the approach.

As a side chain of the work, an economic and efficient procedure for benzyl D_3-vinyl ether synthesis was proposed. Transformation of the readily available calcium carbide, deuterium oxide and benzyl alcohol in the presence of a base and a small admixture of DMSO-d_6, with 1,4-dioxane as a solvent, leads to benzyl D_3-vinyl ether in excellent yield and with ≥96% deuterium incorporation. Probably, further use of this approach can afford a wide range of D_3-vinyl derivatives with no side exchange processes.

Experimental Section

General: All chemicals were purchased from Sigma Aldrich, Alfa Aesar and Acros Organics in reagent grade or better quality and used without further purification. Hydrazonoyl chlorides were synthesized by the procedure reported previously.[25] D-vinyl ether was synthesized by the method of Basu and Marnett.[26] NMR spectra were recorded on a Bruker Avance III spectrometer (^{1}H 400 MHz; ^{13}C 101 MHz, ^{19}F 376 MHz). Chemical shifts δ are reported in ppm relative to residual $CHCl_3$ (^{1}H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.16) as internal standard. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF 10223 spectrometer using electrospray ionization (ESI). Reactions were monitored by TLC analysis using Merck UV-254 plates. Preparative column chromatography was performed on Merck silica gel 60 (230-400 Mesh) that was previously treated with triethylamine.

Computational details

ORCA 4.2.1 program package[27] was used to perform restricted Kohn-Sham and Hartree-Fock calculations. Only (S)-enantiomers were modeled. Gas-phase geometry optimizations were performed at the GFN2-xTB level of theory.[28] Vibrational frequency analysis was conducted to check whether the obtained geometries were true energy minima, and no imaginary frequencies were encountered. The calculated vibrational frequencies were used in the calculations of gas-phase Gibbs free energies within the ideal gas-QRRHO approximation.[29]

Transition state structures were determined as follows. First, a coarse reaction path was generated by invoking the NEB procedure with initial path generation at the GFN2-xTB level.[30] The highest energy point in the reaction path was used for transition state optimization at the GFN2-xTB level. All transition states exhibited one imaginary mode with vibration vector directed along the reaction path, according to post-optimization normal mode analysis.

Single-point calculations with the B97-3c method[23] were performed for quick evaluation of energies for the GFN2-xTB-optimized geometries. Resolution of the identity (RI) approximation[31] and, accordingly, the auxiliary basis set def2-mTZVP/J[23] were used in the B97-3c calculations. Tight convergence criteria were set for the KS-SCF procedure ("TightSCF" option). We selected a dense integration grid for the energy evaluations (GRID6) and switched off the FINALGRID option.

Single-point energy evaluations at the ωB97X-V/def2-TZVP-gCP level[32] was also performed. In these calculations, we applied the RIJCOSX approximation and, implicitly, used the Def2/J auxiliary basis set.[33] The non-local dispersion energy terms were evaluated self-consistently. The "GridX9" and "vdwgrid4" parameters were set; all other parameters were used without change from the previous settings.

Mulliken charges were computed in single-point calculations within the restricted Hartree-Fock formalism at the ZINDO/S level[34] using the structures optimized with the GFN2-xTB method, as described above. Tight convergence criteria were set in the SCF procedure by setting the "TightSCF" option.

Bulk solvent effects were accounted for by applying the SMD model.[35] The M06-2X functional and the 6-31+G** basis set[36] were used in KS-SCF equation solving. Due to the absence of 6-31+G** parameters for Br, we selected the LANL2DZ basis set[37] in this case; hence, a certain decrease in accuracy may be expected for the molecules with Br substituents. In SMD calculations, the RIJCOSX approximation and the Def2/J basis set were used. The grid density and convergence criteria were used without change from the previous settings. The Gibbs free energies of solvation were calculated as a difference between the total energies of molecules with the SMD option switched on and off. Free energies of species in solution (G^A) were calculated according to equation given below:

$$G^A = E^A + \Delta G^A_{QRRHO} + \Delta G^A_{solv} + \Delta G_{conc},$$

Where E^A is the total energy of a molecule A computed at the ωB97X-V/def2-TZVP-gCP level, ΔG^A_{QRRHO} is the sum of thermochemical corrections computed with GFN2-xTB method within the ideal gas, quasi-rigid rotor, and harmonic oscillator approximations,[29] and ΔG_{conc} is the correction term that is equal to 1.89 kcal/mol. The latter term accounts for the change of the system state from the ideal gas at 298 K and 1 atm to the 1 M solution.

Optimized geometries and visualizations of imaginary modes (for transition states) are available in XYZ format in Supporting Information (zip archive). Additional calculations were performed to confirm a good correspondence between geometries optimized with DFT (B97-3c) and tight binding (GFN2-xTB) methods (described in Supporting Information).

General procedure for the synthesis of pyrazoles

The reaction tube was loaded with 1.0 mmol of vinyl ether **2**, **7** or **8** and hydrazonoyl chloride **1a-o** (1.5 mmol). Then, 2 ml of dry benzene and 1.5 mmol of triethylamine were added, the tube was sealed and heated at 80 °C for 24 hours. After, the solvent was evaporated, and the resulting pyrazole was purified by column chromatography (SiO_2, hexane/ethyl acetate 10:1).

3-(4-(*tert*-butyl)phenyl)-1-phenyl-1*H*-pyrazole 3a. Using the general procedure **3a** was obtained in 90 % yield (248 mg). R_f 0.38. Beige solid; m.p. 103-105 °C (lit. 103-105 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.94 (d, *J* = 2.5 Hz, 1H, H_{pyr}), 7.86 (d, *J* = 8.5 Hz, 2H), 7.80-7.77 (m, 2H), 7.49-7.45 (m, 4H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 1H, H_{pyr}), 1.38 (s, 9H, ^{t}Bu). ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 153.1 (C), 151.2 (C), 140.4 (C), 130.5 (C), 129.5 (2CH), 128.0 (CH), 126.3 (CH), 125.73 (2CH), 125.69 (2CH), 119.1 (2CH), 105.1 (CH_{pyr}), 34.8 ($\underline{C}(CH_3)_3$), 31.5 ($3CH_3$). HRMS (ESI) Calcd. for $C_{19}H_{21}N_2^+$ $[M+H]^+$ 277.1699, found 277.1693.

1-phenyl-3-(4-tolyl)-1*H*-pyrazole 3b. Using the general procedure **3b** was obtained in 99 % yield (231 mg). R_f 0.35. Beige solid; m.p. 92-93 °C (lit. 92-94 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.84 (d, J = 8.1 Hz, 2H), 7.80-7.77 (m, 2H), 7.50-7.45 (m, 2H), 7.31-7.25 (m, 3H), 6.75 (d, J = 2.5 Hz, 1H, H_{pyr}), 2.41 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (C=N), 140.4 (C), 137.9 (C), 130.5 (C), 129.50 (2CH), 129.46 (2CH), 128.0 (CH), 126.3 (CH), 125.9 (2CH), 119.1 (2CH), 105.0 (CH_{pyr}), 21.4 (CH_3). HRMS (ESI) Calcd. for $C_{16}H_{15}N_2^+$ $[M+H]^+$ 235.1230, found 235.1230.

3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole 3c. Using the general procedure **3c** was obtained in 97 % yield (242 mg). R_f 0.23. Beige solid; m.p. 101-103 °C (lit. 101-103°C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.86 (d, J = 8.8 Hz, 2H, C_6H_4), 7.77 (d, J = 7.7 Hz, 2H, $H^{2,6}$(Ph)), 7.46 (t, J = 8.0 Hz, 2H, $H^{3,5}$(Ph)), 7.30-7.26 (m, 1H, H^4(Ph)), 6.98 (d, J = 8.8 Hz, 2H, C_6H_4), 6.71 (d, J = 2.5 Hz, 1H, H_{pyr}), 3.86 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (C), 152.9 (C), 140.4 (C), 129.5 (2CH), 128.0 (CH), 127.2 (2CH), 126.3 (CH), 126.1 (C), 119.1 (2CH), 114.2 (2CH), 104.7 (CH_{pyr}), 55.4 (OCH_3). HRMS (ESI) Calcd. for $C_{16}H_{15}N_2O^+$ $[M+H]^+$ 251.1179, found 251.1173.

1,3-diphenyl-1H-pyrazole 3d. Using the general procedure **3d** was obtained in 96 % yield (211 mg). R_f 0.33. Beige solid; m.p. 82-84 °C (lit. 82-85 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (m, 3H), 7.80-7.77 (m, 2H), 7.50-7.43 (m, 4H), 7.38-7.33 (m, 1H), 7.32-7.28 (m, 1H), 6.79 (d, J = 2.5 Hz, 1H, H_{pyr}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1(C=N), 140.4 (C), 133.3 (C), 129.5 (2CH), 128.8 (2CH), 128.14 (CH), 128.09 (CH), 126.4 (CH), 126.0 (2CH), 119.2 (2CH), 105.1 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{13}N_2^+$ $[M+H]^+$ 221.1073, found 221.1072.

3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole 3e. Using the general procedure **3e** was obtained in 93 % yield (277 mg). R_f 0.30. Beige solid; m.p. 123-125 ° C (lit. 122-124 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.79 (d, J = 8.5 Hz, 2H), 7.77-7.75 (m, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.47 (t, J = 8.0 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 2.5 Hz, 1H, H_{pyr}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C=N), 140.3 (C), 132.3 (C), 131.9 (2CH), 129.6 (2CH), 128.3 (CH), 127.5 (2CH), 126.7 (CH), 122.1 (C), 119.2 (2CH), 105.1 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{12}N_2Br^+$ $[M+H]^+$ 299.0178, found 299.0174.

3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole 3f. Using the general procedure **3f** was obtained in 91 % yield (241 mg). R_f 0.15. Beige solid; m.p. 134-136 °C (lit. 134-136 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 9.0 Hz, 2H), 8.07 (d, J = 9.0 Hz, 2H), 8.01 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.80-7.77 (m, 2H), 7.52-7.47 (m, 2H), 7.37-7.33 (m, 1H), 6.87 (d, J = 2.5 Hz, 1H, H_{pyr}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (C=N), 147.4 (C), 140.0 (C), 139.5 (C), 129.7 (2CH), 128.8 (CH), 127.2 (CH), 126.4 (2CH), 124.3 (2CH), 119.4 (2CH), 106.0 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{11}N_3O_2Na^+$ $[M+Na]^+$ 288.0743, found 288.0739.

3-(3,4-dichlorophenyl)-1-phenyl-1*H*-pyrazole 3g. Using the general procedure **3g** was obtained in 88 % yield (254 mg). R_f 0.28. Beige solid; m.p. 94-97 °C (lit. 95-97 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 1.9 Hz, 1H), 7.96 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.77-7.72 (m, 3H), 7.50-7.46 (m, 3H), 7.32 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 2.5 Hz, 1H, H_{pyr}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (C=N), 140.1 (C), 133.4 (C), 133.0 (C), 131.9 (C), 130.7 (CH), 129.6 (2CH), 128.5 (CH), 127.7 (CH), 126.9 (CH), 125.1 (CH), 119.3 (2CH), 105.2 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{11}N_2Cl_2^+$ $[M+H]^+$ 289.0294, found 289.0292.

3-phenyl-1-(4-tolyl)-1*H*-pyrazole 3h. Using the general procedure **3h** was obtained in 88 % yield (206 mg). R_f 0.34. Beige solid; m.p. 110-112 ° C (lit. 111-112 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.93 (m, 2H), 7.91 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.66 (d, J = 8.5 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.37-7.32 (m, 1H), 7.27 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 2.5 Hz, 1H, H_{pyr}), 2.40 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (C=N), 138.2 (C), 136.3 (C), 133.4 (C), 130.0 (2CH), 128.8 (2CH), 128.0 (CH_{Ph}+CH_{pyr}), 125.9 (2CH), 119.2 (2CH), 104.9 (CH_{pyr}), 21.1 (CH_3). HRMS (ESI) Calcd. for $C_{16}H_{15}N_2^+$ $[M+H]^+$ 235.1230, found 235.1230.

1-(4-bromophenyl)-3-phenyl-1*H*-pyrazole 3i. Using the general procedure **3i** was obtained in 89 % yield (265 mg). R_f 0.29. Beige solid; m.p. 133-134 °C (lit. 133-134 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90 (m, 3H), 7.67 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 8.9 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.37-7.33 (m, 1H), 6.79 (d, J = 2.5 Hz, 1H, H_{pyr}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (C=N), 139.4 (C), 133.0 (C), 132.6 (2CH), 128.8 (2CH), 128.4 (CH), 128.0 (CH), 126.0 (2CH), 120.5 (2CH), 119.6 (C), 105.6 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{12}N_2Br^+$ $[M+H]^+$ 299.0178, found 299.0176.

1-(4-fluorophenyl)-3-phenyl-1*H*-pyrazole 3j. Using the general procedure **3j** was obtained in 99 % yield (240 mg). R_f 0.29. Beige solid; m.p. 91-93 °C (lit. 90-92 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H), 7.88 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.76-7.70 (m, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.37-7.33 (m, 1H), 7.19-7.13 (m, 2H), 6.77 (d, J = 2.5 Hz, 1H, H_{pyr}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2 (d, J = 245.6 Hz, CF), 153.2 (C=N), 136.8 (d, J = 2.9 Hz, C), 133.1 (C), 128.8 (2CH), 128.23 (CH), 128.22 (CH), 126.0 (2CH), 120.9 (d, J = 8.3 Hz, 2CH), 116.3 (d, J = 23.0 Hz, 2CH), 105.2 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{12}N_2F^+$ $[M+H]^+$ 239.0979, found 239.0975.

1,3-di(4-tolyl)-1*H*-pyrazole 3k. Using the general procedure **3k** was obtained in 77 % yield (191 mg). R_f 0.35. White solid; m.p. 138 ° C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.81 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.27-7.22 (m, 4H), 6.72 (d, J = 2.5 Hz, 1H, H_{pyr}), 2.39 (s, 6H, $2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (C=N), 138.1 (C), 137.9 (C), 136.3 (C), 130.4 (C), 130.0 (2CH), 129.5 (2CH), 128.1 (CH_{pyr}), 125.9 (2CH), 119.2 (2CH), 104.7 (CH_{pyr}), 21.4 (CH_3), 21.1 (CH_3). HRMS (ESI) Calcd. for $C_{17}H_{17}N_2^+$ $[M+H]^+$ 249.1386, found 249.1374.

3-(4-methoxyphenyl)-1-(4-tolyl)-1*H*-pyrazole 3l. Using the general procedure **3l** was obtained in 89 % yield (235 mg). R_f 0.24. White solid; m.p. 157-158 ° C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.85 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 2.5 Hz, 1H, H_{pyr}), 3.85 (s, 3H, OMe), 2.39 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (C), 152.6 (C=N), 138.1 (C), 136.1 (C), 130.0 (2CH), 128.0 (CH_{pyr}), 127.3 (2CH), 126.1 (C), 119.1 (2CH), 114.2 (2CH), 104.4 (CH_{pyr}), 55.5 (OMe), 21.1 (CH_3). HRMS (ESI) Calcd. for $C_{17}H_{17}N_2O^+$ $[M+H]^+$ 265.1335, found 265.1335.

1-(4-fluorophenyl)-3-(4-tolyl)-1*H*-pyrazole 3m. Using the general procedure **3m** was obtained in 99 % yield (250 mg). R_f 0.33. Colorless solid; m.p. 119-121 ° C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 2.5 Hz, 1H, H_{pyr}), 7.81 (d, J = 8.1 Hz, 2H), 7.74-7.70 (m, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.15 (t, J = 8.6 Hz, 2H), 6.74 (d, J = 2.5 Hz, 1H, H_{pyr}), 2.40 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, J = 245.5 Hz, CF), 153.2 (C=N), 138.0 (C), 136.8 (d, J = 2.8 Hz, C), 130.3 (C), 129.5 (2CH), 128.1 (CH_{pyr}), 125.8 (2CH), 120.8 (d, J = 8.3 Hz, 2CH), 116.3 (d, J = 22.9 Hz, 2CH), 105.0 (CH_{pyr}), 21.41 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.3 ppm. HRMS (ESI) Calcd. for $C_{16}H_{14}FN_2^+$ $[M+H]^+$ 253.1136, found 253.1135.

4,5-dideutero-3-(4-(*tert*-butyl)phenyl)-1-phenyl-1*H*-pyrazole 4a. Using the general procedure **4a** was obtained in 95 % yield (264 mg). R_f 0.38. Beige solid; m.p. 101-102 °C (lit. 100-102 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.89 (m, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.52-7.46 (m, 4H), 7.30 (t, J = 7.4 Hz, 1H), 1.41 (s, 9H, ^{t}Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0 (C), 151.1 (C), 140.4 (C), 130.5 (C), 129.5 (2CH), 127.6 (t, J = 27.6 Hz, CD), 126.3 (CH), 125.71 (2CH), 125.66 (2CH), 119.0 (2CH), 104.7 (t, J = 26.6 Hz, CD), 34.7 ($\underline{C}(CH_3)_3$), 31.4 ($3CH_3$). HRMS (ESI) Calcd. for $C_{19}H_{19}D_2N_2^+$ $[M+H]^+$ 279.1825, found 279.1824.

4,5-dideutero-1-phenyl-3-(4-tolyl)-1*H*-pyrazole 4b. Using the general procedure **4b** was obtained in 99 % yield (234 mg). R_f 0.35. Beige solid; m.p. 92-94 °C (lit. 93-94 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.1 Hz, 2H), 7.79-7.76 (m, 2H), 7.49-7.45 (m, 2H), 7.31-7.24 (m, 3H), 2.41 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (C=N), 140.4 (C), 137.9 (C), 130.5 (C), 129.51 (2CH), 129.47 (2CH), 127.7 (t, J = 27.8 Hz, CD), 126.3 (CH), 125.9 (2CH), 119.1 (2CH), 104.7 (t, J = 26.5 Hz, CD), 21.4 (CH_3). HRMS (ESI) Calcd. for $C_{16}H_{12}D_2N_2Na^+$ $[M+Na]^+$ 259.1175, found 259.1175.

4,5-dideutero-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole 4c. Using the general procedure **4c** was obtained in 97 % yield (244 mg). R_f 0.23. Beige solid; m.p. 100-101 °C (lit. 100-101°C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 2H, C_6H_4), 7.78-7.76 (m, 2H), 7.47 (t, J = 8.0 Hz, 2H, $H^{3,5}$(Ph)), 7.28 (t, J = 7.5 Hz, 1H, H^4(Ph)), 6.99 (d, J = 8.8 Hz, 2H, C_6H_4), 3.86 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7 (C), 152.8 (C), 140.4 (C), 129.5 (2CH), 127.7 (t, J = 28.2 Hz, CD), 127.2 (2CH), 126.2 (CH), 126.1 (C), 119.0 (2CH), 114.2 (2CH), 104.3 (t, J = 26.9 Hz, CD), 55.4 (OCH_3). HRMS (ESI) Calcd. for $C_{16}H_{12}D_2N_2ONa^+$ $[M+Na]^+$ 275.1124, found 275.1116.

4,5-dideutero-1,3-diphenyl-1*H*-pyrazole 4d. Using the general procedure **4d** was obtained in 97 % yield (213 mg). R_f 0.33. Beige solid; m.p. 83-84 °C (lit. 83-85 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.4 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.50-7.44 (m, 4H), 7.37 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0 (C=N), 140.3 (C), 133.3 (C), 129.5 (2CH), 128.8 (2CH), 128.1 (CH), 127.8 (t, J = 29.2 Hz, CD), 126.4 (CH), 125.9 (2CH), 119.1 (2CH), 104.8 (t, J = 27.1 Hz, CD). HRMS (ESI) Calcd. for $C_{15}H_{11}D_2N_2^+$ $[M+H]^+$ 223.1199, found 223.1202.

3-(4-bromophenyl)-4,5-dideutero-1-phenyl-1*H*-pyrazole 4e. Using the general procedure **4e** was obtained in 93 % yield (280 mg). R_f 0.29. Beige solid; m.p. 124-125 °C (lit. 123-125 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.6 Hz, 2H), 7.78-7.74 (m, 2H), 7.56 (d, J = 8.6 Hz, 2H), 7.47 (t, J = 8.0 Hz, 2H), 7.33-7.28 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C=N), 140.2 (C), 132.2 (C), 131.9 (2CH), 129.6 (2CH), 128.0 (t, J = 27.0 Hz, CD), 127.5 (2CH), 126.6 (CH), 122.0 (C), 119.2 (2CH), 104.8 (t, J = 27.2 Hz, CD). HRMS (ESI) Calcd. for $C_{15}H_9BrD_2N_2Na^+$ $[M+Na]^+$ 323.0123, found 323.0134.

4,5-dideutero-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole 4f. Using the general procedure **4f** was obtained in 85 % yield (228 mg). R_f 0.15. Beige solid; m.p. 135-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.6 Hz, 2H), 8.05 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (C), 147.3 (C), 139.9 (C), 139.5 (C), 129.6 (2CH), 128.5 (t, J = 27.7, CD), 127.1 (CH), 126.3 (2CH), 124.2 (2CH), 119.3 (2CH), 105.6 (d, J = 27.3 Hz, CD). HRMS (ESI) Calcd. for $C_{15}H_9D_2N_3O_2Na^+$ $[M+Na]^+$ 290.0869, found 290.0867.

4,5-dideutero-3-phenyl-1-(4-tolyl)-1*H*-pyrazole 4h. Using the general procedure **4h** was obtained in 96 % yield (227 mg). R_f 0.34. Beige solid; m.p. 104-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.28-7.26 (m, 2H), 2.41 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7 (C=N), 138.1 (C), 136.2 (C), 133.4 (C), 130.0 (2CH), 128.7 (2CH), 128.0 (CH), 127.7 (t, J = 27.9 Hz, CD), 125.9 (2CH), 119.1 (2CH), 104.5 (t, J = 26.8 Hz, CD), 21.0 (CH_3). HRMS (ESI) Calcd. for $C_{16}H_{13}D_2N_2^+$ $[M+H]^+$ 237.1355, found 237.1356.

1-(4-bromophenyl)-4,5-dideutero-3-phenyl-1*H*-pyrazole 4i. Using the general procedure **4i** was obtained in 90 % yield (270 mg). R_f 0.29. Beige solid; m.p. = 137-138 °C (lit. 137-138 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.89 (m, 2H), 7.66 (d, J = 9.0 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.45 (t, J = 7.4 Hz, 2H), 7.38-7.33 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (C=N), 139.3 (C), 133.0 (C), 132.5 (2CH), 128.8 (2CH), 128.3 (CH), 127.7 (t, J = 28.4 Hz, CD), 126.0 (2CH), 120.4 (2CH), 119.5 (C), 105.2 (t, J = 26.6 Hz, CD). HRMS (ESI) Calcd. for $C_{15}H_9D_2BrN_2Na^+$ $[M+Na]^+$ 323.0123, found 323.0126.

4,5-dideutero-1,3-di(4-tolyl)-1*H*-pyrazole 4k. Using the general procedure **4k** was obtained in 66 % yield (170 mg). R_f 0.35. Beige solid; m.p. 140-142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.27-7.23 (m, 4H), 2.40 (s, 6H, $2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (C=N), 138.2 (C), 137.8 (C), 136.2 (C), 130.5 (C), 130.0 (2CH), 129.5 (2CH), 127.7 (t, J = 28.3 Hz, CD), 125.9 (2CH), 119.1 (2CH), 104.4 (t, J = 26.9 Hz, CD), 21.4 (CH_3), 21.1 (CH_3). HRMS (ESI) Calcd. for $C_{17}H_{14}D_2N_2Na^+$ $[M+Na]^+$ 273.1331, found 273.1325.

4,5-dideutero-1-(4-fluorophenyl)-3-(4-tolyl)-1*H*-pyrazole 4m. Using the general procedure **4m** was obtained in 99 % yield (250 mg). R_f 0.33. Beige solid; m.p. 119-121 ° C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.1 Hz, 2H), 7.75-7.69 (m, 2H), 7.26 (d, J = 7.9 Hz, 2H), 7.18-7.12 (m, 2H), 2.41 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (d, J = 245.5 Hz, CF), 153.1 (C=N), 138.0 (C), 136.7 (d, J = 2.8 Hz, C), 130.3 (C), 129.5 (2CH), 127.8 (d, J = 28.8 Hz, CD), 125.8 (2CH), 120.8 (d, J = 8.3 Hz, 2CH), 116.2 (d, J = 23.0 Hz, 2CH), 104.7 (d, J = 26.8 Hz, CD), 21.4 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.3 ppm. HRMS (ESI) Calcd. for $C_{16}H_{11}D_2FN_2^+$ $[M+H]^+$ 255.1261, found 255.1262.

5-deutero-3-(4-(*tert*-butyl)phenyl)-1-phenyl-1*H*-pyrazole 9a. Using the general procedure **9a** was obtained in 90 % yield (250 mg). Deuterium incorporation corresponded to **8** (91%). R_f 0.38. Beige solid; m.p. 99-101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 2.5 Hz, 0.09H, residual H-5), 7.89 (d, J = 8.5 Hz, 2H), 7.81-7.77 (m, 2H), 7.51-7.45 (m, 4H), 7.32-7.27 (m, 1H), 6.76 (s, 1H, H-4), 1.40 (s, 9H, ^{t}Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (C=N), 151.2 (C), 140.4 (C), 130.5 (C), 129.5 (2CH), 127.7 (t, J = 28.6 Hz, CD), 126.3 (CH), 125.71 (2CH), 125.67 (2CH), 119.1 (2CH), 104.9 (CH_{pyr}), 34.8 ($\underline{C}Me_3$), 31.5 ($C\underline{Me}_3$). HRMS (ESI) Calcd. for $C_{19}H_{20}DN_2^+$ $[M+H]^+$ 278.1762, found 278.1759.

5-deutero-1,3-diphenyl-1*H*-pyrazole 9d. Using the general procedure **9d** was obtained in 95 % yield (210 mg). Deuterium incorporation corresponded to **8** (91%). R_f 0.33. Beige solid; m.p. 78-80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.8 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.50-7.44 (m, 4H), 7.37 (t, J = 7.3 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 6.79 (s, 1H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0 (C=N), 140.3 (C), 133.3 (C), 129.5 (2CH), 128.8 (2CH), 128.1 (CH), 127.9 (t, J = 27.2 Hz, CD), 126.4 (CH), 126.0 (2CH), 119.1 (2CH), 105.0 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{12}DN_2^+$ $[M+H]^+$ 222.1136, found 222.1133.

5-deutero-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole 9f. Using the general procedure **9f** was obtained in 89 % yield (237 mg). Deuterium incorporation corresponded to **8** (91%). R_f 0.15. Beige solid; m.p. 137-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H), 8.00 (d, J = 2.5 Hz, 0.09H, residual H-5), 7.77 (d, J = 8.0 Hz, 2H), 7.50 (t, J = 7.9 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 6.86 (s, 1H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (C=N), 147.4 (C), 140.0 (C), 139.5 (C), 129.7 (2CH), 128.6 (t, J = 28.4 Hz, CD), 127.1 (CH), 126.3 (2CH), 124.2 (2CH), 119.3 (2CH), 105.9 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{10}DN_3O_2Na^+$ $[M+Na]^+$ 289.0806, found 289.0806.

1-(4-bromophenyl)-5-deutero-3-phenyl-1*H*-pyrazole 9i. Using the general procedure **9i** was obtained in 91 % yield (273 mg). Deuterium incorporation corresponded to **8** (91%). R_f 0.30. Beige solid; m.p. 135-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2.09H, $2H_{Ar}$ and the residual H-5), 7.66 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 8.9 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.38-7.34 (m, 1H), 6.78 (s, 1H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4 (C=N), 139.3 (C), 133.0 (C), 132.5 (2CH), 128.8 (2CH), 128.3 (CH), 127.7 (t, J = 28.7 Hz, CD), 126.0 (2CH), 120.4 (2CH), 119.5 (C), 105.4 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_{10}DBrN_2Na^+$ $[M+Na]^+$ 322.0061, found 322.0066.

5-deutero-1-(2,6-dichlorophenyl)-3-phenyl-1*H*-pyrazole 9o. Using the general procedure **9o** was obtained in 93 % yield (269 mg). R_f 0.23.

Deuterium incorporation corresponded to **8** (91%). Beige solid; m.p. 106-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H), 7.58 (d, J = 2.5 Hz, 0.09H, residual H-5), 7.48-7.41 (m, 4H), 7.36-7.32 (m, 2H), 6.82 (s, 1H, H-4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2 (C=N), 136.6 (C), 134.8 (2C), 133.0 (C), 132.8 (t, J = 28.9 Hz, CD), 130.7 (CH), 128.8 (2CH), 128.7 (2CH), 128.2 (CH), 126.1 (2CH), 104.0 (CH_{pyr}). HRMS (ESI) Calcd. for $C_{15}H_9DCl_2N_2Na^+$ $[M+Na]^+$ 312.0176, found 312.0181.

General procedure for the synthesis of benzyl D_3-vinyl ether 2b

The reaction tube was loaded with 128 mg (2.0 mmol) of CaC_2, 78 mg (0.7 mmol) of KO^{t}Bu, 52 mg (0.9 mmol) of KF and 76 mg (72 µl, 0.7 mmol) of benzyl alcohol. Then, 1 ml of dry 1,4-dioxane, DMSO-d_6 (120 µl), and 72 µl (4.0 mmol) of water were added, the tube was immediately sealed and heated at 110 °C for 4 hours. After, the reaction mixture was poured to 10 ml of water and extracted five times with 7 ml of hexane. The combined organic extracts were washed three times with water, dried over sodium sulfate and evaporated on rotary evaporated to give benzyl D_3-vinyl ether **2b** in 94% yield (90 mg) as a colorless oil. ^{1}H NMR (400 MHz, C_6D_6) δ 7.18-7.04 (m, 5H, Ph), 4.45 (s, 2H, CH_2). ^{13}C NMR (101 MHz, C_6D_6) δ 151.6 (t, J = 27.8 Hz, =CD), 137.5 (C), 128.6 (2CH), 127.9 (CH), 127.7 (2CH), 86.6 (quint, J = 24.3 Hz, $=CD_2$), 70.0 (CH_2). HRMS (ESI) Calcd. for $C_9H_7D_3OAg^+$ $[M+Ag]^+$ 243.9965, found 243.9967.

Decyl 1-deuterovinyl ether 8. Was synthesized by the previously reported procedure.[26] Yield 472 mg (75%). Colorless oil. ^{1}H NMR (400 MHz, C_6D_6) δ 6.46 (dd, J = 14.4, 6.8 Hz, 0.09H, residual OCH=), 4.18 (s, 1H from $=CH_2$), 3.96 (s, 1H from $=CH_2$), 3.47 (t, J = 6.5 Hz, 2H, OCH_2), 1.56-1.48 (m, 2H), 1.32-1.21 (m, 14H), 0.91 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, C_6D_6) δ 152.2 (t, J = 27.7 Hz, CD), 85.9 (CH_2), 67.9 (CH_2), 32.3 (CH_2), 30.00 (CH_2), 29.99 (CH_2), 29.8 ($2CH_2$), 29.5 (CH_2), 26.4 (CH_2), 23.1 (CH_2), 14.4 (CH_3). HRMS (ESI) Calcd. for $C_{12}H_{23}DOAg^+$ $[M+Ag]^+$ 294.0932, found 294.0940.

4-methyl-*N*-(*p*-tolyl)benzohydrazonoyl chloride 1k. Was synthesized by the previously reported procedure.[25] Yield 387 mg (60%). Colorless solid, m.p. 121-123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 1H, NH), 7.81 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.13-7.06 (m, 4H), 2.39 (s, 3H, CH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (C), 139.4 (C), 132.0 (C), 130.5 (C), 130.0 (2CH), 129.2 (2CH), 126.4 (2CH), 124.5 (C), 113.5 (2CH), 21.4 (CH_3), 20.8 (CH_3). HRMS (ESI) Calcd for $C_{15}H_{15}ClN_2Na^+$ $[M+Na]^+$ 281.0816, found 281.0807.

4-methoxy-*N*-(*p*-tolyl)benzohydrazonoyl chloride 1l. Was synthesized by the previously reported procedure.[25] Yield 433 mg (64%). Colorless solid, m.p. 134-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.85 (m, 3H, NH+$2CH_{Ar}$), 7.12 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6 (C), 141.5 (C), 130.3 (C), 130.0 (2CH), 128.0 (2CH), 127.5 (C), 124.3 (C), 113.9 (2CH), 113.5 (2CH), 55.5 (OCH_3), 20.8 (CH_3). HRMS (ESI) calcd for $C_{16}H_{19}N_2O_2^+$ $[M–Cl+MeOH]^+$ 271,1441, found: 271,1454.

***N*-(4-fluorophenyl)-4-methylbenzohydrazonoyl chloride 1m.** Was synthesized by the previously reported procedure.[25] Yield 191 mg (87%). Colorless solid, m.p. 70-72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H, NH), 7.80 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.14-7.09 (m, 2H), 7.01 (t, J = 8.7 Hz, 2H), 2.39 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9 (d, J = 238.8 Hz, CF), 140.0 (d, J = 2.2 Hz, C), 139.6 (C), 131.8 (C), 129.3 (2CH), 126.5 (2CH), 125.3 (C), 116.1 (d, J = 22.8 Hz, 2CH), 114. 6 (d, J = 7.6 Hz, 2CH), 21.4 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ -123.5 ppm.

Acknowledgements

We gratefully acknowledge financial support from the Russian Science Foundation (Project № 19-73-10032).

The authors express their gratitude to the Resource Centres of Saint Petersburg State University: Magnetic Resonance Research Centre, Chemical Analysis and Materials Research Centre, Computing Centre.

Keywords: cycloaddition • deuterium • deuteropyrazole • isotopic labeling • vinyl ether

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10.1002/ejoc.202000674

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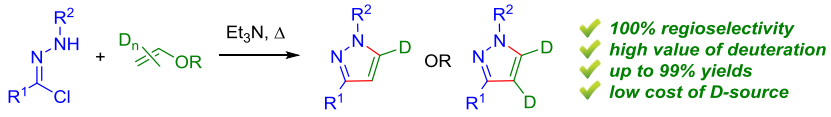

A novel synthetic path to 1,3-disubstituted pyrazoles, 4,5-dideuteropyrazoles and 5-deuteropyrazoles based on the interaction of the readily available vinyl ethers and *in situ* generated nitrile imines was developed. The joint experimental and computational study clarified the mechanism of the process and allowed us to propose a convenient access to regioselectively deuterated pyrazoles.

Keywords: cycloaddition • deuterium • deuteropyrazole • isotopic labeling • vinyl ether