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Rubazonic Acids and Their Synthesis

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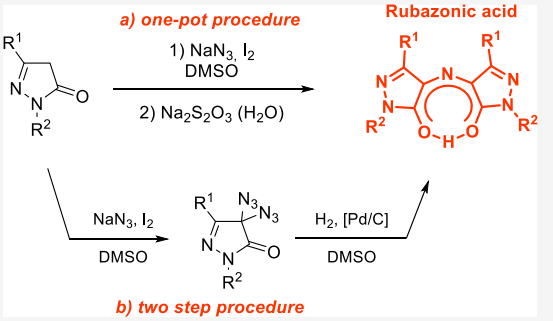
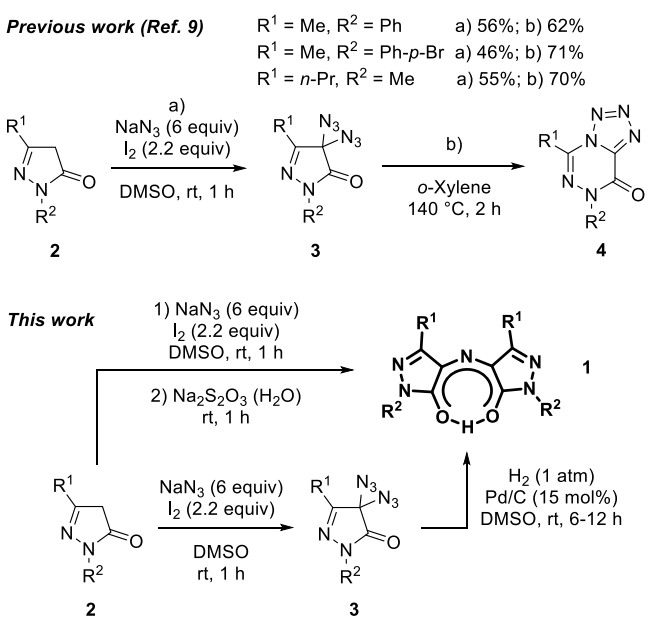
ABSTRACT: Rubazonic acids are a class of dyes that are long-known, but studies on their syntheses and uses are rare. We now describe an experimentally simple and highly practical one-pot procedure for their synthesis starting from easily accessible 1*H*-pyrazol-5(4*H*)-ones. This protocol provides direct access to a broad range of the desired rubazonic acid derivatives through oxidative diazidation combined with a reductive work-up, without the need to isolate the potentially hazardous diazido compounds generated *en route* the target compounds. We also show how more challenging variants of rubazonic acid are efficiently prepared using an alternative two-step procedure and controlled hydrogenation conditions.



INTRODUCTION

In the last few years, we are highly involved in studying the synthesis and reactivity of small organic molecules possessing geminal diazido units.[1−7] In this context, we looked into the synthesis of tetrazolotriazinones **4** through the thermolysis of 4,4-diazidopyrazolones **3** (Scheme 1),[8] and it was found that the yields for the formation of the geminal diazides **3** through oxidative diazidation of the 1*H*-pyrazol-5(4*H*)-ones **2** were surprisingly low, although our standard reaction conditions with iodine and sodium azide in aqueous dimethyl sulfoxide (DMSO) had been widely successful with many related substrate classes: under typical aqueous work-up conditions using $Na_2S_2O_3$ as the reductive agent to quench the excess of iodine, most of the initially generated diazido compound **3** was lost and deeply red-colored phases were obtained, instead. The careful analysis of the colored phases lets us assume that the color originates from the relatively smooth conversion of diazide **3** into the rubazonic acids **1**, under reductive work-up conditions.

Scheme 1. Synthesis and Reactivity of Diazidopyrazolones



Rubazonic acid **1a** (R^1 = Me and R^2 = Ph) was described for the first time by Knorr in 1887:[9] It is a red-colored dye, which exhibits a symmetrical structure with a strong intramolecular hydrogen bond.[10] This acidic proton has a characteristic ^{1}H NMR shift at around 17.4 ppm (in $CDCl_3$)[11] and the crystal structure analysis shows an almost linear O−H−O bond.[12] Despite the fact that rubazonic acids are known for over a century, there still is a major lack of practical methods allowing for their synthesis. Most synthetic attempts toward rubazonic acids, even recently, are based on the original protocols reported by Knorr, which require the *in situ* formation of labile 4-amino-pyrazolinones (e.g., from 4-nitroso-4,5-dihydro-1*H*-pyrazol-5-ones),[13] followed by some variant of oxidation. Alternative methods[14−16] tested only with a few singular examples are rare and typically low-yielding, including the use of azomethine precursors,[11] 4-chloroimino-4,5-dihydro-1*H*-pyrazol-5-ones,[17] 1*H*-pyrazole-4,5-diones,[18] or through the direct conversion of pyrazolones with diazo transfer.[12]

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This lack of synthetic methods is more surprising because there are a few reports implying that rubazonic acids **1** may have a great potential as functional dyes in material sciences, for example, as chemical sensors, biological markers, or optical materials. Characteristic absorbance was observed for the coordination of transition metals with rubazonic acid **1a**[12,19] and stable complexes are also formed with heavy metals.[11] Rubazonic acids were also neglected with regard to the involvement of hydrogen-assisted resonance bonding, a useful concept in the design of functional materials,[20] although they possess this aforementioned unique hydrogen bond in connection with the π-conjugated system. Early uses of rubazonic acid **1a** for the colorimetric determination of ammonia and cyanate were discontinued.[21−23]

We were spurred by the missed potential of rubazonic acids and, therefore, we decided to elaborate on our unexpected formation of rubazonic acids **1** through the diazidation of pyrazolones **2**. Herein, we now report an experimentally simple and highly practical one-pot procedure for the rubazonic acid synthesis starting from easily accessible 1*H*-pyrazol-5(4*H*)-ones. A broad and highly useful scope is presented together with preliminary studies on UV/vis absorption, with the goal to trigger anew research activities in this field, resulting in the development of applications.

RESULTS AND DISCUSSION

Synthesis of Rubazonic Acid Derivatives. We began our studies with the optimization of the one-pot reaction conditions providing rubazonic acids **1** from pyrazolones **2** through a sequence consisting of diazidation and subsequent reductive work-up. It was found that the best yields were typically achieved using the standardized reaction conditions summarized in Scheme 2: A solution of pyrazolone, iodine (2.2. equiv), and sodium azide (6 equiv) in DMSO is stirred at room temperature (for 60−90 min), followed by the addition of saturated aqueous sodium thiosulfate solution. This experimentally simple protocol led to the formation of rubazonic acid **1a** in 81% yield. The substrate scope was then studied by varying the pyrazolone positions 1 (R^2) and 3 (R^1). When testing the pyrazolones with R^1 being alkyl and R^2 being aryl, the corresponding rubazonic acids **1a−1f** were typically obtained in good yields (>80%; *e.g.*, **1a**, **1b**, and **1f**). In the case of rubazonic acid **1c**, we observed a reduced yield, most likely due to the more sterically demanding isopropyl group R^1. In the case of the bromo-substituted rubazonic acid derivative **1d**, we had unexpected issues with the solubility, and only trace amounts of the pure compound were isolated and used for the characterization by mass spectrometry and ^{1}H NMR spectroscopy. Although the conversion toward **1d** appeared to proceed smoothly (according to TLC), the material was constantly lost in the course of multiple attempts of purification. To our delight, the longer chain variant **1e** (R^1 = *n*-butyl) was markedly more soluble in organic solvents and could be obtained with an isolated yield of 52%.

Pyrazolones with R^1 = Ph were also successfully converted into the corresponding rubazonic acids, albeit with markedly lowered yields (**1g−i**). In the case of R^1 = Ph and R^2 = *t*-Bu, not even traces of the desired dye **1j** were obtained. We concluded that the phenyl groups interfere with the rubazonic acid formation in a severe way, allowing side reactions to occur: for example, the generation of small amounts of the imine species **5** was observed by ^{1}H NMR and mass analysis in all reactions where substrates with R^1 = Ph were subjected to diazidation conditions. The imine **5i** was isolated in 10% yield and fully characterized, even though this compound tended to quickly decompose at room temperature. Of note, a related generation of imines through the treatment of malonate-derived geminal diazides with reducing agents was previously described by us.[24] Pyrazolones with two alkyl substituents (R^1, R^2 = alkyl) also provided the corresponding rubazonic acids **1k−m** with only moderate yields ranging from 51 to 70%.

Assuming that the diazidated pyrazolones **3** are the key intermediates on the route to rubazonic acids **1** via the one-pot protocol outlined above, we then decided to study the reductive dimerization **3a** → **1a**. As summarized in Table 1,

Scheme 2. Synthesis of Rubazonic Acids 1 from Pyrazolones 2

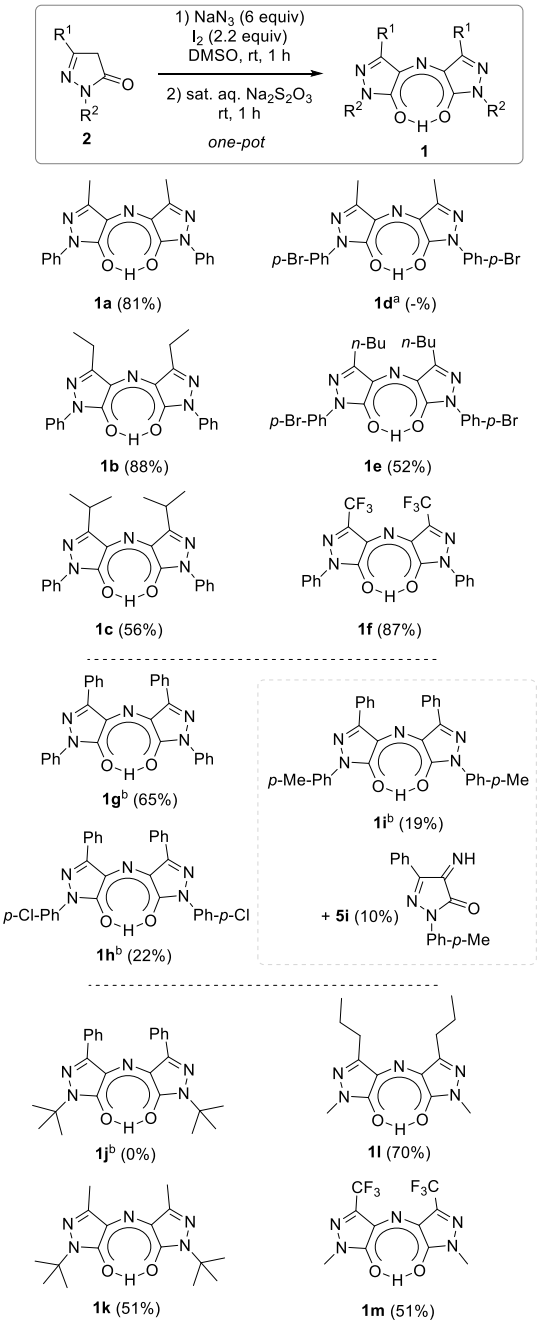

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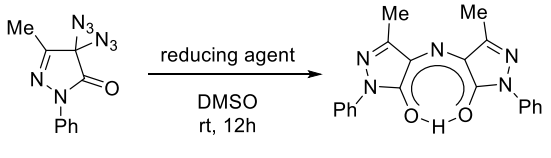
Table 1. Testing Reducing Agents for the Synthesis of Rubazonic Acid 1a



3a 1a

entry	reducing agent	yield (%)[a]
1	$Na_2S_2O_3$	38
2	PPh_3	31
3	$NaBH_4$	47
4	H_2, Pd/C	85

[a]Isolated yields after column chromatography.

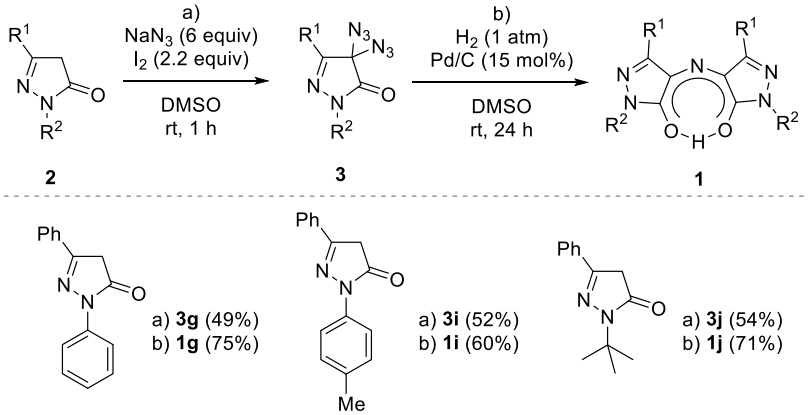
several reducing agents were tested in terms of efficacy, with the goal to identify the optimum conditions. It was found that the use of sodium thiosulfate only yielded 38% of the desired compound **1a**. Consequently, we reasoned that the high yields afforded for the rubazonic acid formation through the one-pot sequence are explained best with the need for an incomplete conversion of the pyrazolones, followed by aqueous work-up rather than with fully diazidated intermediates. With respect to our synthetic method toward rubazonic acids, this surprising result underlined the importance of keeping the reaction times of the diazidation step fairly short. Other classes of reducing agents were also effective: for example, sodium boronhydride and triphenylphosphine delivered the rubazonic acid in 47 and 31%, respectively. The best results, however, were achieved with dihydrogen and 15 mol % of palladium on charcoal under atmospheric pressure giving **1a** in an excellent yield of 85%. The latter conditions were practically free from side products, thus resulting in a greatly simplified purification process.

We then sought to access rubazonic acids **1** from pyrazolones **2** through a new two-step procedure that involves diazidated intermediates **3** (i.e., **2** → **3** → **1**). The initial oxidative diazidation appeared to be straightforward using our established conditions with sodium azide and iodine in DMSO (in the absence of work-up with $Na_2S_2O_3$).[2] In combination with the high-yielding hydrogenolysis of diazidated pyrazolones, the formation of the rubazonic acids **1g**, **1i**, and **1j** was achieved, all of which performed poorly with our original one-pot protocol. As shown in Scheme 3, the pyrazolone diazidation afforded the diazido intermediates **3g**, **3i**, and **3j** in yields between 46 and 54%. The subsequent reduction with dihydrogen provided the rubazonic acid **1j** with 71% yield, a compound that was not obtained with the one-pot procedure. Moreover, rubazonic acids **1g** and **1i** were accessed with significantly improved yields of 60 and 75%, thus demonstrating certain advantages of using the two-step synthetic route toward rubazonic acids.

Although in terms of conditions and scope, our experiments are a thorough groundwork for the synthesis of valuable amounts of rubazonic acid dyes, the studies on mechanistic aspects were less convincing, unfortunately. We currently believe that several parallel pathways exist that provide rubazonic acids from pyrazolones when merging oxidative azidating conditions with reductive conditions. As outlined in Scheme 4A, hydrogenolysis of diazidated pyrazolone **3g** results in rubazonic acid formation, most likely through condensation of imine (**A**) and amino (**B**) intermediates of different oxidation states as originally proposed by Knorr.[9] Our previous studies on the hydrogenolysis of other classes of geminal diazides somewhat support this assumption by showing that imines are the primary products of hydrogenation but further reduction to amines is easy.[24] The analogous reduction with thiosulfates was less effective, although possible. Indeed, the existence of imine intermediates of type **A** was observed in the course of several rubazonic acid syntheses, and imine **5i** was isolated (*vide supra*). We note that efficient rubazonic acid formation then involves (i) a potent conversion of diazide **3** into imine **A** and (ii) a rapid reaction between amine **B** and imine **A** forming **1** (i.e., in steady competition with the ongoing reduction **A** → **B**).

To explain the high yields of our one-pot route toward rubazonic acids (using thiosulfate as the terminal reducing agent), we were actively looking for an alternative pathway. Based on our previous results on oxidative diazidations with sodium azide-iodine mixtures in DMSO,[2] the occurrence of monoazidated pyrazolone intermediates (besides diazides **3** and the starting pyrazolones **1**) was ruled out: for all compound classes we studied so far in diazidation processes, the second azidation *en route* to diazides was found to be significantly more rapid than the first one; careful analysis of the reaction mixtures of pyrazolone diazidation did not provide any clues pointing to possible monoazidated compounds. We were also not able to find evidence for the *in situ* formation of monoiodinated or diiodinated pyrazolones, under the conditions. To our surprise, however, we discovered an

Scheme 3. Two-Step Protocol for the Synthesis of Rubazonic Acids 1g, 1i, and 1j



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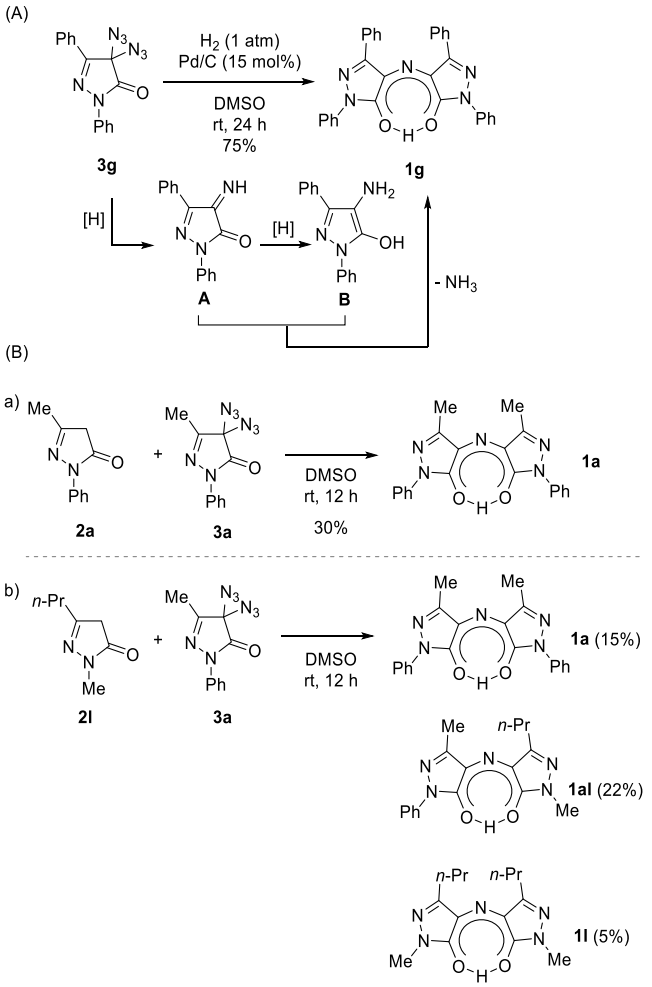
Scheme 4. Mechanistic Assumptions and the Reaction of Diazidopyrazolone 3a with (a) Pyrazolone 2a and (b) Pyrazolone 2l



uncommon internal redox process between pyrazolones **1** and the diazidated congeners **3** that leads to rubazonic acid formation and may account for the good yields of our one-pot protocol, at least partially. As shown in Scheme 4B, pyrazolone **2a** and diazidated pyrazolone **3a** reacted in DMSO at room temperature to give the rubazonic acid **1a** in 30% yield, with no additional reagents added. The geminal diazide **3a**, on the other hand, is perfectly stable in DMSO over a couple of days, and the red dye is not formed. Although we are currently not able to propose a useful mechanistic explanation, this experiment indicates that the pyrazolone **2a** acts as the reducing agent for diazide **3a**, may be in analogy to better known radical functionalizations of pyrazolones.[25−29] Even more strikingly, the reaction of diazide **3a** with pyrazolone **2l** provided a mixture of three rubazonic acids, the dimeric compounds **1a** and **1l**, and the mixed product **1al**. We conclude that at one point of the reaction, a nitrogen atom is transferred from the diazido reagent onto the simple pyrazolone, the mechanism of which is under further investigation. However, the rubazonic acid, once formed, is fully stable and does not undergo exchange reactions with either diazides **3**, pyrazolones **2**, or imines **5**.

The existence of parallel pathways may explain how good yields of rubazonic acids are achieved even when the conversion into the diazide intermediates is incomplete because of relatively short reaction times for the diazidation step (approximately 90 min): the diazidated pyrazolones can combine with either diazidated pyrazolones or nonazidated pyrazolones to finally provide the rubazonic acids.

UV/Vis Spectroscopy of Rubazonic Acids. A range of rubazonic acids were tested with regard to the effect of the pre-eminent intramolecular hydrogen bond on IR and NMR spectra.[10] Surprisingly, systematic studies of UV/vis absorption are rare, although the most evident feature of the rubazonic acid dyes is their color.[22] Absorption spectra were mainly reported for rubazonic acid **1a** (R^1 = Me and R^2 = Ph), and the pH dependency of the absorption maxima was studied in aqueous solutions: **1a** exhibits three principal absorption maxima at λ_1 = 540 nm, λ_2 = 442 nm, and λ_3 = 340 nm.[12] Under basic conditions, the λ_2 band fully disappears. On the other hand, λ_3 shifts bathochromically to 350 nm under acidic conditions, and there is no absorption band at 540 nm.[19]

We also briefly examined the absorption properties of selected rubazonic acid dyes **1** using UV/vis spectroscopy, with the goal to make this class of compounds more attractive to researchers of adjacent fields. As shown in Figure 1A, our absorption spectra of rubazonic acid **1a** in MeCN/H_2O (1:1) over a wide pH range (from 1 to 13.8) paralleled the earlier measurements by others. When acidified, **1a** absorbs mainly in the region around 450 nm, which correlates with a heavily orange color of the dye. The color changes to deep purple between pH 5 and pH 6, and **1a** exhibits absorption maxima at 540 and 340 nm in basic solution. We concluded that the existence of the H bridge is a major contributor to the orange color of the dyes; deprotonation results in an increased electron density in the conjugated system that is accompanied by the violet appearance. Accordingly, substituents at the rubazonic acid core have a great influence on the color at

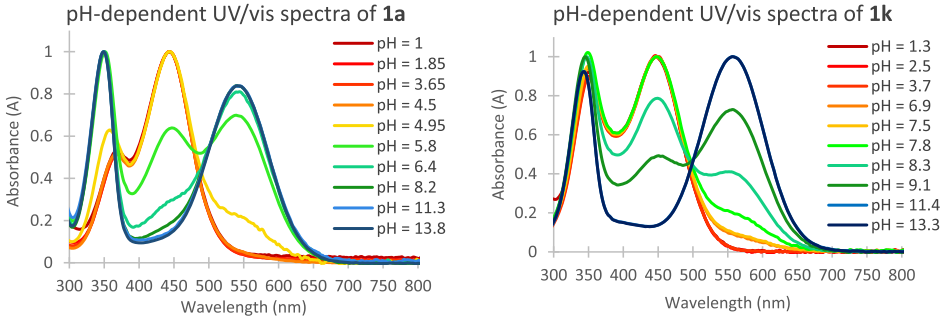


Figure 1. Normalized pH-dependent UV/vis absorption spectra of rubazonic acid **1a** (A) and **1k** (B); c = 1 mg/100 mL; compounds dissolved in H_2O/MeCN (1:1); addition of 1 M HCl/1 M NaOH.

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certain pH values. For example, we found that rubazonic acid **1k** (R^1 = Me and R^2 = *t*-Bu) changes the color between pH 7.8 and pH 8.8 meaning that this dye remains orange over a significantly expanded pH range (Figure 1B).

The dielectric constant and the hydrogen bonding capacity of solvents were also expected to influence the intramolecular hydrogen bond of rubazonic acids and thus the color of the dyes. Figure 2 shows how the orange-colored rubazonic acid **1a**

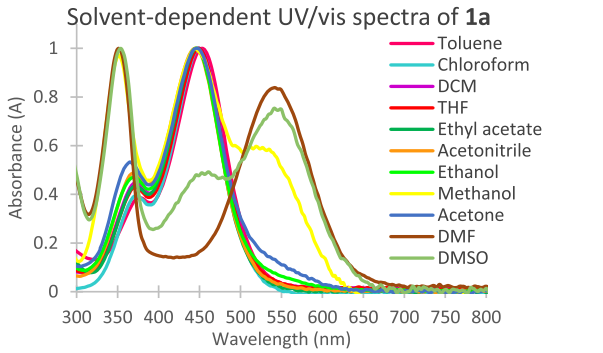

Figure 2. Normalized solvent-dependent UV/vis absorption spectra of rubazonic acid (**1a**); *c* = 1 mg/100 mL; compounds solved in H_2O/MeCN (1:1).

possesses a very similar absorption behavior in rather unpolar solvents (*i.e.*, toluene, chloroform, dichloromethane, tetrahydrofuran, ethyl acetate, and acetonitrile) and in protic solvents (*i.e.*, ethanol) with an absorption maximum at around 450 nm. In aprotic polar solvents (*i.e.*, DMF and DMSO), a solvatochromic effect occurs, and the characteristic absorption band at around 550 nm was detected.

The UV/vis spectra of all rubazonic acids presented by us herein (**1a** − **1m** + **1al**) were recorded in DCM and in dimethylformamide (DMF). Table 2 summarizes the absorption maxima found in the visible region and in the UV region. In DCM, all absorption maxima (of the visible region) were observed between 446 and 467 nm. The corresponding absorption maxima in DMF were ranging from 449 to 589 nm, depending on the exact structure of the rubazonic acid. As exemplified for **1k** (R^1 = Me and R^2 = *t*-Bu) in Figure 3, the doubly alkyl-substituted rubazonic acids are typically blue-shifted compared to the doubly aryl-substituted derivatives, in both solvents. In fact, **1k** (and **1l**) was the only rubazonic acid from our portfolio that had the characteristic absorption around 450 nm in DMF attributed to the existence of the intramolecular hydrogen bond, while the rubazonic acids **1a**, **1g** (R^1 = Ph and R^2 = Ph), and **1j** (R^1 = Ph and R^2 = *t*-Bu) show absorption maxima between 542 and 589 nm in DMF. These effects were significantly smaller in DCM with 452 nm for **1k** and 464 nm for **1g**. However, solutions of rubazonic acids in DCM are heavily influenced by the substituents R^1 and R^2 in the UV region where **1k** exhibits an absorption maximum at 352 nm and **1g** has a red-shifted band peak at 382 nm.

Table 2. UV/Vis Absorption Maxima of Rubazonic Acid Derivatives 1 in DCM and DMF; *c* = 1 mg/100 mL

				DCM		DMF	
entry	compound	R^1	R^2	λ^{UV}_{max} (nm)	λ^{Vis}_{max} (nm)	λ^{UV}_{max} (nm)	λ^{Vis}_{max} (nm)
1	**1a**	Me	Ph	372	449	351	542
2	**1b**	Et	Ph	375	452	351	540
3	**1c**	*i*-Pr	Ph	375	455	351	541
4	**1d**	Me	Ph-*p*-Br	375	452	351	540
5	**1e**	*n*-Bu	Ph-*p*-Br	377	456	351	543
6	**1f**	CF_3	Ph	378	451	351	553
7	**1g**	Ph	Ph	382	464	363	574
8	**1h**	Ph	Ph-*p*-Cl	385	467	364	569
9	**1i**	Ph	Ph-*p*-Me	383	466	367	578
10	**1j**	Ph	*t*-Bu	374	459	363	460, 589
11	**1k**	Me	*t*-Bu	352	452	350	452
12	**1l**	*n*-Pr	Me	351	449	349	449
13	**1m**	CF_3	Me	339	465	333	409, 556
14	**1al**	Me, *n*-Pr	Me, Ph	361	446	345	546

SUMMARY

In conclusion, we described two highly practical protocols for the generation of rubazonic acids **1**, a convenient one-pot protocol that applies to most examples and a two-step protocol for the more challenging rubazonic acid derivatives. Both methods provide the desired dyes through the controlled formation of diazido intermediates, starting with easily accessible 1*H*-pyrazol-5(4*H*)-ones. Preliminary experiments on the mechanism of rubazonic acid formation under our conditions indicate that parallel pathways contribute to product formation, and further studies by us are currently underway. We also reported on the interesting UV−vis absorption of several rubazonic acid derivatives: The absorbance is clearly influenced by the substituents attached to the pyrazolone core, and strong solvent effects and a pH dependency were demonstrated. We therefore encourage researchers to use this underdeveloped but promising class of compounds; rubazonic acids may be considered as dyes for material sciences or as sensors for analytical sciences.

EXPERIMENTAL SECTION

General Remarks. The commercial reagents and solvents were used as received. All reactions were operated under air and no measures were taken to exclude water. In all reactions with elevated temperatures, an oil bath was used as a heat source. Thin-layer chromatography (TLC) was conducted with aluminum sheets (TLC silica gel 60 F_{254}) and visualized by exposure to UV light (254 nm), stained with ceric ammonium molybdate (CAM) or basic potassium permanganate ($KMnO_4$) and subsequent heating. Flash column chromatography was performed on silica gel (40−60 μm), and the eluent used is reported in the respective experiments. Abbreviations of solvents are as follows: PE: petroleum ether, EA: ethyl acetate, DCM: dichloromethane, and CH: cyclohexane. IR spectra were measured using an attenuated total reflection (ATR) technique in the range of 400−4000 cm^{-1}. ^1H NMR spectra were recorded with 400 or 600 MHz instruments, and ^{13}C NMR spectra were recorded at 101 or 151 MHz. Chemical shifts are reported as δ values in ppm relative to the solvent signal and coupling constants *J* in Hz. Multiplicities were defined by standard abbreviations. Low-resolution mass spectra (LRMS) were recorded using an LC/MS-combination (ESI). High-resolution mass spectra (HRMS) were obtained using ESI ionization on a Bruker micrOTOF or FD ionization on a JEOL-TOF. UV/vis spectra were obtained with a Mettler Toledo spectrophotometer.

Caution! Geminal diazides are potentially hazardous and should be handled with care. Although we never encountered any problems, we advise the use of protective gear, in particular, for scales >1 mmol.

General Procedures. *General Procedure A for the Synthesis of Diazidopyrazolones* **3**. The pyrazolone **2** (1.0 equiv) was dissolved in DMSO (0.15 M), and sodium azide (6.0 equiv) and iodine (2.2

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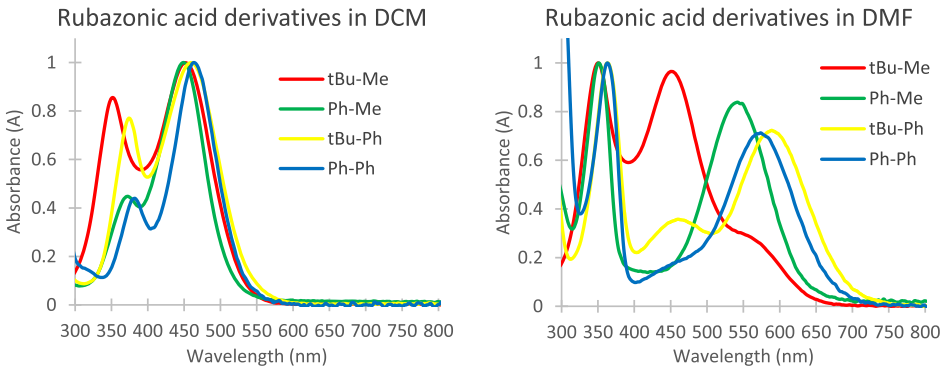

Figure 3. Normalized UV/vis absorption spectra of rubazonic acid derivatives **1a** (Ph−Me), **1g** (Ph−Ph), **1j** (*t*-Bu−Ph), and **1k** (*t*-Bu−Me) in DCM and DMF; c = 1 mg/100 mL.

equiv) were subsequently added. The reaction mixture was stirred at room temperature for 90 min. An equal volume of water and a few drops of saturated aqueous sodium thiosulfate solution were added carefully (until the color of iodine disappears), and the mixture was immediately extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and purification by flash chromatography on silica gel afforded the corresponding diazidopyrazolones **3**.

*General Procedure B for the Synthesis of Rubazonic Acids **1**.* The pyrazolone **2** (1.0 equiv) was dissolved in DMSO (0.15 M), and sodium azide (6 equiv) and iodine (2.2 equiv) were added. The reaction mixture was stirred at room temperature for 90 min. Then, an excess of saturated aqueous sodium thiosulfate solution was added, and the mixture was heavily stirred at room temperature for 1 h. The mixture was extracted with dichloromethane and the combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and purification by flash chromatography on silica gel afforded the corresponding rubazonic acids **1**.

*General Procedure C for the Synthesis of Rubazonic Acids **1**.* The diazidopyrazolone **3** (1.0 equiv) was dissolved in DMSO (0.15 M), and palladium on activated charcoal (10%, 0.15 equiv) was added. The reaction mixture was stirred at room temperature under hydrogen atmosphere (1 atm) until completion of the reaction (as monitored by TLC) and filtered through celite. Water was added, and the mixture was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and purification by flash chromatography on silica gel afforded the corresponding rubazonic acids **1**.

*Synthesis of Pyrazolones **2**.* Pyrazolones **2a**, **2f**, **2l**, and **2m** were commercially available. Other pyrazolones **2** were synthesized using known literature methods.[30−32]

*1-(4-Bromphenyl)-3-butyl-1H-pyrazol-5(4H)-one (**2e**).* (4-Bromphenyl)hydrazine hydrochloride (1.50 g, 6.64 mmol, 1.0 equiv) and methyl 3-oxoheptanoate (1.05 g, 6.64 mmol, 1.0 equiv) were dissolved in 11 mL of acetic acid (0.6 M). The reaction mixture was stirred at 120 °C for 10 h. The solvent was removed under reduced pressure, and purification by flash chromatography on silica gel (DCM) afforded 1-(4-bromphenyl)-3-butyl-1*H*-pyrazol-5(4*H*)-one (0.912 g, 3.09 mmol, 47%) (**2e**) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83−7.77 (m, 2H), 7.51−7.46 (m, 2H), 3.40 (s, 2H), 2.49 (t, J = 7.9 Hz, 2H), 1.63 (p, J = 7.4 Hz, 2H), 1.42 (h, J = 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H) [ppm]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 170.6, 160.5, 137.4, 131.9, 120.3, 117.8, 41.9, 31.1, 28.7, 22.5, 13.9 [ppm]. LRMS (ESI) m/z (%): 591 (21), 295 (100) $[M + H]^+$. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}BrN_2O$, 295.0441; found, 295.0440. IR (ATR): $\tilde{\nu}$ = 3092, 2956, 2930, 2871, 2861, 1717, 1612, 1561, 1488, 1328, 1073, 1008, 825, 714, 501 [cm^{-1}].

*Synthesis of Diazidopyrazolones **3**.* The synthesis of diazidopyrazolone **2a** was published recently.[8]

*4,4-Diazido-1,3-diphenyl-1H-pyrazol-5(4H)-one (**3g**).* According to general procedure A using 150 mg of 0.635 mmol 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**2g**), 4,4-diazido-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (98.7 mg, 0.311 mmol, 49%) (**3g**) was obtained as a red solid after chromatography (CH → CH/DCM 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04−7.97 (m, 4H), 7.55−7.51 (m, 1H), 7.52−7.47 (m, 4H), 7.31 (tt, J = 7.4, 1.1 Hz, 1H) [ppm]. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 164.2, 153.0, 136.9, 132.0, 129.3, 129.1, 127.6, 127.4, 126.5, 119.2, 76.8 [ppm]. LRMS (ESI) m/z (%): 659 (45), 319 (100) $[M + H]^+$, 221 (58). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{10}N_8NaO$, 341.0870; found, 341.0869. IR (ATR): $\tilde{\nu}$ = 3066, 2926, 2854, 2107, 1721, 1597, 1491, 1392, 1246, 1185, 963, 936, 754, 688 [cm^{-1}].

*4,4-Diazido-3-phenyl-1-(p-tolyl)-1H-pyrazol-5(4H)-one (**3i**).* According to general procedure A using 300 mg of 1.20 mmol 3-phenyl-1-(*p*-tolyl)-1*H*-pyrazol-5(4*H*)-one (**2i**), 4,4-diazido-3-phenyl-1-(*p*-tolyl)-1*H*-pyrazol-5(4*H*)-one (205 mg, 0.617 mmol, 52%) (**3i**) was obtained as a red solid after chromatography (CH → CH/DCM 7:3). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07−7.97 (m, 2H), 7.88−7.84 (m, 2H), 7.54−7.46 (m, 3H), 7.31−7.26 (m, 2H), 2.40 (s, 3H) [ppm]. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 164.1, 152.9, 136.4, 134.5, 131.9, 129.8, 129.0, 127.7, 127.3, 119.2, 76.7, 21.2 [ppm]. LRMS (ESI) m/z (%): 333 (100) $[M + H]^+$, 235 (49). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{12}N_8NaO$, 355.1026; found, 355.1023. IR (ATR): $\tilde{\nu}$ = 3038, 2924, 2863, 2119, 1722, 1512, 1392, 1246, 1189, 963, 937, 816, 688 [cm^{-1}].

*4,4-Diazido-1-(tert-butyl)-3-phenyl-1H-pyrazol-5(4H)-one (**3j**).* According to general procedure A using 115 mg of 0.532 mmol 1-(*tert*-butyl)-3-phenyl-1-pyrazol-5(4*H*)-one (**2j**), 4,4-diazido-1-(*tert*-butyl)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (86 mg, 0.29 mmol, 54%) (**3j**) was obtained as yellow oil after chromatography (CH → CH/DCM 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91−7.83 (m, 2H), 7.49−7.39 (m, 3H), 1.61 (s, 9H) [ppm]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 166.1, 150.9, 131.2, 128.9, 128.2, 126.8, 76.6, 59.6, 28.2 [ppm]. LRMS (ESI) m/z (%): 299 (100) $[M + H]^+$, 172 (20). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{14}N_8NaO$, 321.1183; found, 321.1196. IR (ATR): $\tilde{\nu}$ = 3062, 2981, 2936, 2103, 1713, 1560, 1449, 1369, 1201, 1109, 944, 760, 688, 652, 599 [cm^{-1}].

Synthesis of Rubazonic Acids 1. *4-((5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)imino)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**1a**).* According to general procedure B using 100 mg of 0.574 mmol 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2a**), rubazonic acid **1a** (83.1 mg, 231 μmol, 81%) was obtained as a red solid after chromatography (DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 17.44 (s, 1H), 7.94−7.88 (m, 4H), 7.48−7.42 (m, 4H), 7.32−7.26 (m, 2H), 2.34 (s, 6H) [ppm]. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 154.5, 152.4, 137.7, 129.0, 126.9, 125.9, 120.8, 12.0 [ppm]. LRMS (ESI) m/z (%): 360 (100) $[M + H]^+$. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}N_5O_2$, 360.1455; found, 360.1459. IR (ATR): $\tilde{\nu}$ = 3066, 2993, 2953, 2923, 2853, 1594, 1539, 1493, 1373, 1325, 1011,

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757, 687 [cm^{-1}]. UV/vis (DCM): λ_{max} = 372, 449; (DMF): λ_{max} = 351, 542 [nm]. The analytical data are in accordance with the literature values.[10]

*3-Ethyl-4-((3-ethyl-5-hydroxy-1-phenyl-1H-pyrazol-4-yl)imino)-1-phenyl-1H-pyrazol-5(4H)-one (**1b**).* According to general procedure B using 50 mg of 0.27 mmol 3-ethyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2b**), rubazonic acid **1b** (45.2 mg, 117 μmol, 88%) was obtained as a red solid after chromatography (CH/DCM 1:1 → DCM). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 17.38 (s, 1H), 7.95−7.91 (m, 4H), 7.50−7.41 (m, 4H), 7.33−7.27 (m, 2H), 2.79 (q, *J* = 7.5 Hz, 4H), 1.36 (t, *J* = 7.6 Hz, 6H) [ppm]. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 158.7, 152.6, 137.8, 129.1, 127.0, 125.3, 121.0, 20.4, 12.2 [ppm]. LRMS (ESI) *m*/*z* (%): 388 (100) $[M + H]^+$. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{22}N_5O_2$, 388.1768; found, 388.1776. IR (ATR): $\tilde{\nu}$ = 3044, 2971, 2925, 2874, 2853, 1731, 1593, 1582, 1492, 1370, 1091, 753, 687, 479 [cm^{-1}]. UV/vis (DCM): λ_{max} = 375, 452; (DMF): λ_{max} = 351, 540 [nm].

*4-((5-Hydroxy-3-isopropyl-1-phenyl-1H-pyrazol-4-yl)imino)-3-isopropyl-1-phenyl-1H-pyrazol-5(4H)-one (**1c**).* According to general procedure B using 50 mg of 0.25 mmol 3-isopropyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2c**), rubazonic acid **1c** (28.8 mg, 69.3 μmol, 56%) was obtained as a red solid after chromatography (CH/DCM 1:1 → DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 17.26 (s, 1H), 7.98−7.93 (m, 4H), 7.50−7.43 (m, 4H), 7.35−7.25 (m, 2H), 3.27 (hept, *J* = 6.9 Hz, 2H), 1.41 (d, *J* = 7.0 Hz, 12H) [ppm]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 161.6, 152.7, 137.9, 129.1, 126.9, 124.7, 121.0, 27.2, 21.0 [ppm]. LRMS (ESI) *m*/*z* (%): 416 (100) $[M + H]^+$. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{26}N_5O_2$, 416.2081; found, 416.2074. IR (ATR): $\tilde{\nu}$ = 3066, 3047, 2968, 2929, 2871, 1525, 1491, 1369, 986, 754, 687 [cm^{-1}]. UV/vis (DCM): λ_{max} = 375, 455; (DMF): λ_{max} = 351, 541 [nm].

*1-(4-Bromophenyl)-4-((1-(4-bromophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)imino)-3-methyl-1H-pyrazol-5(4H)-one (**1d**).* According to general procedure B using 50 mg of 0.20 mmol 1-(4-bromophenyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**2d**), rubazonic acid **1d** was obtained as a red solid. The insoluble crude product was washed several times with DCM to afford traces of the pure compound for analysis. The compound is too insoluble to record ^{13}C{^{1}H} NMR. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 17.41 (s, 1H), 7.89−7.84 (m, 4H), 7.63−7.56 (m, 4H), 2.35 (s, 6H) [ppm]. LRMS (ESI) *m*/*z* (%): 516 (100) $[M - H]^-$. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{14}Br_2N_5O_2$, 515.9500; found, 515.9501. IR (ATR): $\tilde{\nu}$ = 3102, 2963, 2922, 1542, 1489, 1375, 1330, 1172, 1006, 820, 480 [cm^{-1}]. UV/vis (DCM): λ_{max} = 375, 452; (DMF): λ_{max} = 351, 540 [nm].

*1-(4-Bromophenyl)-4-((1-(4-bromophenyl)-3-butyl-5-hydroxy-1H-pyrazol-4-yl)imino)-3-butyl-1H-pyrazol-5(4H)-one (**1e**).* According to general procedure B using 500 mg of 1.69 mmol 1-(4-bromophenyl)-3-butyl-1*H*-pyrazol-5(4*H*)-one (**2e**), rubazonic acid **1e** (265 mg, 440 μmol, 52%) was obtained as a red solid after chromatography (CH/DCM 7:3 → CH/DCM 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 17.40 (s, 1H), 7.88−7.81 (m, 4H), 7.58−7.52 (m, 4H), 2.75−2.66 (m, 4H), 1.79−1.67 (m, 4H), 1.46 (h, *J* = 7.4 Hz, 4H), 0.98 (t, *J* = 7.3 Hz, 6H) [ppm]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 158.1, 152.4, 136.8, 132.1, 125.4, 122.1, 120.2, 30.3, 26.6, 22.9, 14.0 [ppm]. LRMS (ESI) *m*/*z* (%): 600 (100) $[M - H]^-$. HRMS (ESI-TOF) *m*/*z*: $[M - H]^-$ calcd for $C_{26}H_{26}Br_2N_5O_2$, 600.0440; found, 600.0439. IR (ATR): $\tilde{\nu}$ = 3109, 2955, 2928, 2870, 2858, 1595, 1573, 1530, 1487, 1351, 1007, 826, 484 [cm^{-1}]. UV/vis (DCM): λ_{max} = 377, 456; (DMF): λ_{max} = 351, 543 [nm].

*4-((5-Hydroxy-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)imino)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**1f**).* According to general procedure B using 80 mg of 0.34 mmol 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one (**2f**), rubazonic acid **1f** (70.2 mg, 150 μmol, 87%) was obtained as a red solid after chromatography (CH + 1% AcOH → CH/DCM 9:1 + 1% AcOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 17.12 (s, 1H), 7.91−7.82 (m, 4H), 7.55−7.47 (m, 4H), 7.45−7.34 (m, 2H) [ppm]. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −64.79 [ppm]. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 152.1, 144.6 (q, *J* = 37.5 Hz), 136.6, 129.4, 128.5, 123.4, 121.5, 119.4 (q, *J* = 272.3 Hz) [ppm]. LRMS (ESI) *m*/*z* (%): 466 (100) $[M - H]^-$. HRMS (ESI-TOF) *m*/*z*: $[M - H]^-$ calcd for $C_{20}H_{10}F_6N_5O_2$ 466.0744; found, 466.0743. IR (ATR): $\tilde{\nu}$ = 3069, 2954, 2924, 2854, 1608, 1588, 1588, 1520, 1369, 1151, 969, 870, 759, 728 [cm^{-1}]. UV/vis (DCM): λ_{max} = 378, 451; (DMF): λ_{max} = 351, 553 [nm].

*4-((5-Hydroxy-1,3-diphenyl-1H-pyrazol-4-yl)imino)-1,3-diphenyl-1H-pyrazol-5(4H)-one (**1g**).* According to general procedure B using 100 mg of 0.423 mmol 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**2g**), rubazonic acid **1g** (66.8 mg, 138 μmol, 65%) was obtained as a red solid after chromatography (DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 16.99 (s, 1H), 8.09−7.96 (m, 8H), 7.55−7.48 (m, 4H), 7.49−7.38 (m, 2H), 7.39−7.29 (m, 6H) [ppm]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 152.6, 152.3, 137.7, 130.6, 129.8, 129.3, 129.2, 128.4, 127.4, 125.9, 121.3 [ppm]. LRMS (ESI) *m*/*z* (%): 482 (100) $[M - H]^-$. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{22}N_5O_2$, 484.1768; found, 484.1766. IR (ATR): $\tilde{\nu}$ = 3061, 2955, 2924, 2853, 1564, 1518, 1484, 1456, 1413, 1340, 1307, 961, 754, 689, 668, 493 [cm^{-1}]. UV/vis (DCM): λ_{max} = 382, 464; (DMF): λ_{max} = 363, 574 [nm]. The analytical data are in accordance with the literature values.[10]

*1-(4-Chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-phenyl-1H-pyrazol-4-yl)imino)-3-phenyl-1H-pyrazol-5(4H)-one (**1h**).* According to general procedure B using 50 mg of 0.19 mmol 1-(4-chlorophenyl)-3-phenyl-1*H*-pyrazol-5(4*H*)-one (**2h**), rubazonic acid **1h** (11.4 mg, 20.6 μmol, 22%) was obtained as a red solid after chromatography (CH/DCM 1:1 → CH/DCM 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 17.03 (s, 1H), 8.04−7.97 (m, 4H), 7.97−7.89 (m, 4H), 7.49−7.41 (m, 2H), 7.38−7.30 (m, 8H) [ppm]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 152.8, 152.3, 136.3, 132.9, 130.3, 130.0, 129.4, 129.3, 129.0, 128.5, 122.3 [ppm]. LRMS (ESI) *m*/*z* (%): 552 (100) $[M + H]^+$. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{30}H_{20}Cl_2N_5O_2$, 552.0989; found, 552.0988. IR (ATR): $\tilde{\nu}$ = 2920, 1555, 1516, 1488, 1420, 1338, 960, 856, 754 [cm^{-1}]. UV/vis (DCM): λ_{max} = 385, 467; (DMF): λ_{max} = 364, 569 [nm].

*4-((5-Hydroxy-3-phenyl-1-(p-tolyl)-1H-pyrazol-4-yl)imino)-3-phenyl-1-(p-tolyl)-1H-pyrazol-5(4H)-one (**1i**).* According to general procedure B using 50 mg of 0.20 mmol 3-phenyl-1-(*p*-tolyl)-1*H*-pyrazol-5(4*H*)-one (**2i**), rubazonic acid **1i** (9.5 mg, 19 μmol, 19%) was obtained as a red solid after chromatography (DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 17.03 (s, 1H), 8.04−7.97 (m, 4H), 7.97−7.90 (m, 4H), 7.49−7.42 (m, 2H), 7.38−7.31 (m, 8H), 2.44 (s, 6H) [ppm]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 152.4, 152.1, 137.3, 135.3, 130.7, 129.7, 129.3, 128.4, 125.8, 121.3, 115.0, 21.3 [ppm]. LRMS (ESI) *m*/*z* (%): 512 (100) $[M + H]^+$. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{32}H_{26}N_5O_2$, 512.2081; found, 512.2078. IR (ATR): $\tilde{\nu}$ = 2953, 2920, 2852, 1560, 1508, 1481, 1422, 1341, 1307, 1077, 962, 857, 817, 754, 693, 657, 501 [cm^{-1}]. UV/vis (DCM): λ_{max} = 383, 466; (DMF): λ_{max} = 367, 578 [nm].

*4-Imino-3-phenyl-1-(p-tolyl)-1H-pyrazol-5(4H)-one (**5i**).* According to general procedure B using 50 mg of 0.20 mmol 3-phenyl-1-(*p*-tolyl)-1*H*-pyrazol-5(4*H*)-one (**2i**), 4-imino-3-phenyl-1-(*p*-tolyl)-1*H*-pyrazol-5(4*H*)-one (5.3 mg, 20 μmol, 10%) (**5i**) was obtained as a red solid after chromatography (DCM). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.07 (s, 1H), 8.39−8.31 (m, 2H), 7.90−7.83 (m, 2H), 7.54−7.47 (m, 3H), 7.33−7.23 (m, 2H), 2.39 (s, 3H) [ppm]. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ = 164.5, 150.7, 147.7, 136.0, 135.0, 131.3, 129.8, 128.9, 128.9, 127.6, 118.6, 21 [ppm]. LRMS (ESI) *m*/*z* (%): 264 (100) $[M + H]^+$. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{16}H_{13}N_3NaO$, 286.0951; found, 286.0952. IR (ATR): $\tilde{\nu}$ = 3196, 3070, 2921, 2857, 1719, 1513, 1328, 1154, 1087, 931, 815, 752 [cm^{-1}].

*1-(tert-Butyl)-4-((1-(tert-butyl)-5-hydroxy-3-phenyl-1H-pyrazol-4-yl)imino)-3-phenyl-1H-pyrazol-5(4H)-one (**1j**).* According to general procedure C using 51.3 mg of 0.172 mmol diazidopyrazolone **2j**, rubazonic acid **1j** (27.2 mg, 62.3 μmol, 71%) was obtained as a red solid after chromatography (CH → CH/DCM 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 16.35 (s, 1H), 7.94−7.89 (m, 4H), 7.40−7.33 (m, 2H), 7.32−7.23 (m, 4H), 1.70 (s, 18H) [ppm]. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 153.2, 149.7, 131.5, 129.0, 129.0, 128.2, 125.9, 60.2, 28.4 [ppm]. LRMS (ESI) *m*/*z* (%): 444 (100) $[M + H]^+$.

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HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{30}N_5O_2$, 444.2394; found, 444.2392. IR (ATR): $\tilde{\nu}$ = 3057, 2980, 2930, 1515, 1330, 1211, 864, 755, 691 [cm^{-1}]. UV/vis (DCM): λ_{max} = 374, 459; (DMF): λ_{max} = 363, 460, 589 [nm].

*1-(tert-Butyl)-4-((1-(tert-butyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)imino)-3-methyl-1H-pyrazol-5(4H)-one (**1k**).* According to general procedure B using 50 mg of 0.32 mmol 1-(*tert*-butyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**2k**), rubazonic acid **1k** (26 mg, 82 μmol, 51%) was obtained as a red solid after chromatography (DCM → DCM/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 16.89 (s, 1H), 2.20 (s, 6H), 1.57 (s, 18H) [ppm]. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 153.4, 151.6, 126.0, 59.4, 28.4, 12.0 [ppm]. LRMS (ESI) m/z (%): 320 (100) $[M + H]^+$. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{26}N_5O_2$, 320.2081; found, 320.2071. IR (ATR): $\tilde{\nu}$ = 2987, 2955, 2923, 2853, 1524, 1461, 1367, 1317, 1211, 1052, 756, 617 [cm^{-1}]. UV/vis (DCM): λ_{max} = 352, 452; (DMF): λ_{max} = 350, 452 [nm].

*4-((5-Hydroxy-1-methyl-3-propyl-1H-pyrazol-4-yl)imino)-1-methyl-3-propyl-1H-pyrazol-5(4H)-one (**1l**).* According to general procedure B using 50 mg of 0.35 mmol 1-methyl-3-propyl-1*H*-pyrazol-5(4*H*)-one (**2l**), rubazonic acid **1l** (35.2 mg, 121 μmol, 70%) was obtained as a red solid after chromatography (DCM → DCM/EtOAc 6:4). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 17.25 (s, 1H), 3.50 (s, 6H), 2.58 (t, J = 7.6 Hz, 4H), 1.70 (h, J = 7.4 Hz, 4H), 0.98 (t, J = 7.4 Hz, 6H) [ppm]. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ = 156.6, 153.1, 124.5, 33.2, 28.7, 21.8, 14.2 [ppm]. LRMS (ESI) m/z (%): 292 (100) $[M + H]^+$. HRMS (FD) m/z: $[M]^+$ calcd for $C_{14}H_{21}N_5O_2$, 291.1695; found, 291.1686. IR (ATR): $\tilde{\nu}$ = 2962, 2933, 2875, 2854, 1645, 1581, 1528, 1468, 1388, 1327, 1233, 954, 896, 708, 492 [cm^{-1}]. UV/vis (DCM): λ_{max} = 351, 449; (DMF): λ_{max} = 349, 449 [nm].

*1-Methyl-4-((1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-imino)-3-(trifluoromethyl)-1H-pyrazol-5(4H)-one (**1m**).* According to general procedure B using 77 mg of 0.45 mmol 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-5(4*H*)-one (**2m**), rubazonic acid **1m** (38.8 mg, 114 μmol, 51%) was obtained as a red solid after chromatography (CH + 1% AcOH → CH/DCM 8:2 + 1% AcOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 16.87 (s, 1H), 3.63 (s, 6H) [ppm]. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −64.72 [ppm]. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 153.0, 143.3 (q, J = 37.2 Hz), 122.9, 119.3 (q, J = 271.7 Hz), 34.2 [ppm]. LRMS (ESI) m/z (%): 344 (100) $[M + H]^+$. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_8F_6N_5O_2$, 344.0577; found, 344.0579. IR (ATR): $\tilde{\nu}$ = 2955, 2924, 2854, 1639, 1518, 1472, 1382, 1171, 1060, 879, 720 [cm^{-1}]. UV/vis (DCM): λ_{max} = 339, 465; (DMF): λ_{max} = 333, 409, 556 [nm].

*4-((5-Hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)imino)-1-methyl-3-propyl-1H-pyrazol-5(4H)-one (**1al**).* Pyrazolone **2l** (27 mg, 0.20 mmol, 1 equiv) and diazidopyrazolone **3a** (50 mg, 0.20 mmol, 1 equiv) were dissolved in 1.3 mL of DMSO (0.15 M) and the reaction mixture was stirred for 12 h at room temperature. Water was added, and the mixture was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and purification by flash chromatography on silica gel (DCM → DCM/EtOAc 1:1) afforded rubazonic acid **1al** (13.9 mg, 42.7 μmol, 22%) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 17.16 (s, 1H), 7.95−7.88 (m, 2H), 7.48−7.40 (m, 2H), 7.31−7.25 (m, 1H), 3.55 (s, 3H), 2.65 (t, J = 7.5 Hz, 2H), 2.31 (s, 3H), 1.74 (h, J = 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H) [ppm]. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 157.0, 154.3, 153.5, 152.1, 137.8, 129.1, 127.3, 126.8, 123.1, 33.5, 28.6, 21.7, 14.2, 12.2 [ppm]. LRMS (ESI) m/z (%): 326 (100) $[M + H]^+$. HRMS (FD): m/z = $[M]^+$ calcd for $C_{17}H_{19}N_5O_2$, 325.1539; found, 325.1558. IR (ATR): $\tilde{\nu}$ = 3067, 3048, 2955, 2922, 2869, 2854, 1711, 1637, 1562, 1492, 1370, 1321, 755 [cm^{-1}]. UV/vis (DCM): λ_{max} = 361, 446; (DMF): λ_{max} = 345, 546 [nm].

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00465.

^{1}H and ^{13}C NMR spectra of the selected examples (PDF)

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Notes

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■ REFERENCES

(1) Harschneck, T.; Hummel, S.; Kirsch, S. F.; Klahn, P. Practical Azidation of 1,3-Dicarbonyls. *Chem.—Eur. J.* **2012**, *18*, 1187−1193.

(2) Erhardt, H.; Häring, A. P.; Kotthaus, A.; Roggel, M.; Tong, M. L.; Biallas, P.; Jübermann, M.; Mohr, F.; Kirsch, S. F. Geminal Diazides Derived from 1,3-Dicarbonyls: A Protocol for Synthesis. *J. Org. Chem.* **2015**, *80*, 12460−12469.

(3) Holzschneider, K.; Häring, A. P.; Haack, A.; Corey, D. J.; Benter, T.; Kirsch, S. F. Pathways in the Degradation of Geminal Diazides. *J. Org. Chem.* **2017**, *82*, 8242−8250.

(4) Erhardt, H.; Kunz, K. A.; Kirsch, S. F. Thermolysis of Geminal Diazides: Reagent-Free Synthesis of 3-Hydroxypyridines. *Org. Lett.* **2017**, *19*, 178−181.

(5) Holzschneider, K.; Mohr, F.; Kirsch, S. F. Synthesis and Reactivity of 3,3-Diazidooxindoles. *Org. Lett.* **2018**, *20*, 7066−7070.

(6) Holzschneider, K.; Häring, A. P.; Kirsch, S. F. 2,2-Diazido-1,2-diarylethanones: Synthesis and Reactivity with Primary Amines. *Eur. J. Org. Chem.* **2019**, 2824−2831.

(7) Biallas, P.; Heider, J.; Kirsch, S. F. Functional polyamides with gem-diazido units: synthesis and diversification. *Polym. Chem.* **2019**, *10*, 60−64.

(8) Holzschneider, K.; Tong, M. L.; Mohr, F.; Kirsch, S. F. A Synthetic Route Toward Tetrazoles: The Thermolysis of Geminal Diazides. *Chem.—Eur. J.* **2019**, *25*, 11725−11733.

(9) Knorr, L. Synthetische Versuche mit dem Acetessigester. *Liebigs Ann. Chem.* **1887**, *238*, 137−219.

(10) Bratan-Mayer, S.; Strohbusch, F.; Hänsel, W. IR and NMR-Spectroscopic Studies on Rubazonic Acids. *Z. Naturforsch.* **1976**, *31*, 1106−1115.

(11) Hänsel, W. 4-(5-Hydroxy-4-Pyrazolylimino)-2-Pyrazolin-5-Ones and Their Metal-Chelates1. Synthesis of 4-(5-Hydroxy-4-Pyrazolylimino)-2-Pyrazolin-5-Ones (Rubazoic Acids) and Compounds with Analogous Structures. *Liebigs Ann. Chem.* **1976**, *1976*, 1380−1394.

(12) Cerchiaro, G.; Da Costa Ferreira, A. M.; Teixeira, A. B.; Magalhães, H. M.; Cunha, A. C.; Ferreira, V. F.; Santos, L. S.; Eberlin, M. N.; Skakle, J. M. S.; Wardell, S. M. S. V.; Wardell, J. L. Synthesis and crystal structure of 2,4-dihydro-4-[(5-hydroxy-3methyl-1-phenyl-1H-pyrazol-4-yl)imino]-5-methyl-2-phenyl-3H-pyrazol-3-one and its copper(II) complex. *Polyhedron* **2006**, *25*, 2055−2064.

(13) Ohno, M.; Ido, M.; Shimizu, S.; Eguchi, S. A Facile Synthesis of 2-Phenylimino-3(2H)-benzofuranones from the Silyl Enol Ether of 2-Hydroxyacetophenones and Nitrosobenzene. *Synthesis* **1990**, 703−704.
(14) Barry, V. C.; Mccormick, J. E.; Henseke, G.; Brosche, P.; Demuth, I.; Müller, U.; Engelmann, H.; Crawack, G. über die Bildung einer Rubazonsäure aus Phenylhydrazinderivaten der Zucker. *Eur. J. Org. Chem.* **1961**, 96−113.
(15) Duffin, G. F.; Kendall, J. D. The isomerization of αβ-di(arylhydrazono)-γ-butyrolactones. *J. Chem. Soc.* **1955**, 3969−3971.
(16) Rizk, H. F. Simple and convenient procedures for the synthesis of novel heterocyclic compounds containing 1-phenyl-3-pyridylpyrazole moiety. *Bulg. Chem. Commun.* **2009**, *41*, 241−247.
(17) Lutze, G.; Kirschke, K.; Krauss, N. 1-Arylimino-Pyrazole Betaines, Pyrazoles and 1,2,4-Triazines from 3-Arylazo-Propenoic Acid N-Chloroamides. *J. Prakt. Chem.* **1993**, *335*, 616−622.
(18) Aly, M. F.; El-Nagger, G. M.; El-Emary, T. I.; Grigg, R.; Metwally, S. A. M.; Sivagnanam, S. X-Y-ZH Compounds as potential 1,3-Dipoles. *Tetrahedron* **1994**, *50*, 895−906.
(19) Kovalchukova, O. V.; Strashnova, S. B.; Ilyukhin, A. B.; Sergienko, V. S.; Zaitsev, B. E.; Volyanskii, O. V.; Korolev, O. V.; Dutova, T. Y. Complex compounds of a series of d metals with rubazinic acid (HRub). Crystal and molecular structure of [Co-(H2O)6](NO3)2 · 2HRub. *Russ. J. Coord. Chem.* **2010**, *36*, 751−756.
(20) Mahmudov, K. T.; Pombeiro, A. J. L. Resonance-Assisted Hydrogen Bonding as a Driving Force in Synthesis and a Synthon in the Design of Materials. *Chem.—Eur. J.* **2016**, *22*, 16356−16398.
(21) Kruse, J. M.; Mellon, M. G. Colorimetric Determination of Ammonia and Cyanate. *Anal. Chem.* **1953**, *25*, 1188−1192.
(22) Prochazkova, L. Spectrophotometric Determination of Ammonia as Rubazoic Acid with Bispyrazolone Reagent. *Anal. Chem.* **1964**, *36*, 865−871.
(23) Ballot, A. F. K. B.; Steendijk, C. Ammonia determination in a trichloroacetic acid blood filtrate after microdiffusion with the aid of the rubazonic acid reaction. *Clin. Chim. Acta* **1965**, *12*, 55−62.
(24) Biallas, P.; Kirsch, S. F. Hydrogenolysis of geminal diazides. *Tetrahedron Lett.* **2017**, *58*, 4209−4211.
(25) Nakagawa, H.; Ohyama, R.; Kimata, A.; Suzuki, T.; Miyata, N. Hydroxyl radical scavenging by edaravone derivatives: Efficient scavenging by 3-methyl-1-(pyridin-2-yl)-5-pyrazolone with an intramolecular base. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5939−5942.
(26) Schulz, M.; Meske, M. Radikalreaktionen an N-Heterocyclen. XI [1] Reaktionen von 3-Methyl-pyrazolin-5-onen mit Phenoxyl-Radikalen. *J. Prakt. Chem.* **1993**, *335*, 607−615.
(27) Sheng, X.; Zhang, J.; Yang, H.; Jiang, G. Tunable Aerobic Oxidative Hydroxylation/Dehydrogenative Homocoupling of Pyrazol-5-ones under Transition-Metal-Free Conditions. *Org. Lett.* **2017**, *19*, 2618−2621.
(28) Sun, P.; Yang, D.; Wei, W.; Jiang, L.; Wang, Y.; Dai, T.; Wang, H. DMSO-promoted regioselective synthesis of sulfenylated pyrazoles via a radical pathway. *Org. Chem. Front.* **2017**, *4*, 1367−1371.
(29) Toonchue, S.; Sumunnee, L.; Phomphrai, K.; Yotphan, S. Metal-free direct oxidative C-C bond coupling of pyrazolones and quinoxalinones. *Org. Chem. Front.* **2018**, *5*, 1928−1932.
(30) Sera, M.; Mizufune, H.; Tawada, H. Ligand-free Heck−Mizoroki reaction for 1,3,5-Trisubstituted Pyrazoles. *Tetrahedron* **2015**, *71*, 2833−2838.
(31) Li, H.; Gontla, R.; Flegel, J.; Merten, C.; Ziegler, S.; Antonchick, A. P.; Waldmann, H. Enantioselective Formal C(sp3)−H Bond Activation in the Synthesis of Bioactive Spiropyrazolone Derivatives. *Angew. Chem., Int. Ed.* **2019**, *58*, 307−311.
(32) Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. Direct and Enantioselective Vinylogous Michael Addition of α-Alkylidenepyrazolinones to Nitroolefins Catalyzed by Dual Cinchona Alkaloid Thioureas. *Adv. Synth. Catal.* **2014**, *356*, 2330−2336.

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