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On-Water Vinylogous Mukaiyama–Michael Addition of Heterocyclic 2-Silyloxydienes to 1,2-Diaza-1,3-dienes: One-Pot Three-Step Entry to Functionality-Rich Pyrroles

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Abstract: Densely substituted pyrrole-carboxylates have been prepared in good yields in a highly practical one-pot three-step procedure. The key reaction of this process, which involves an uninterrupted sequence of reactions on-water, is a diastereoselective vinylogous Mukaiyama–Michael addition reaction (VMMcR) of heterocyclic 2-silyloxydienes to 1,2-diaza-1,3-dienes mediated by water itself. Subsequent *in situ* addition of catalytic aqueous sodium carbonate promotes an intramolecular aza-Michael addition with final ring-opening and aromatization. The superior use of water in the VMMcR as both reaction medium and promoter *vis-à-vis* deployment of conventional Lewis acids in organic solvents is highlighted, which provides the best results in terms of reaction rate, efficiency, stereoselectivity, and overall practicality.

Keywords: 1,2-diaza-1,3-dienes; green chemistry; nitrogen heterocycles; silyloxydienes; vinylogous Mukaiyama–Michael reaction

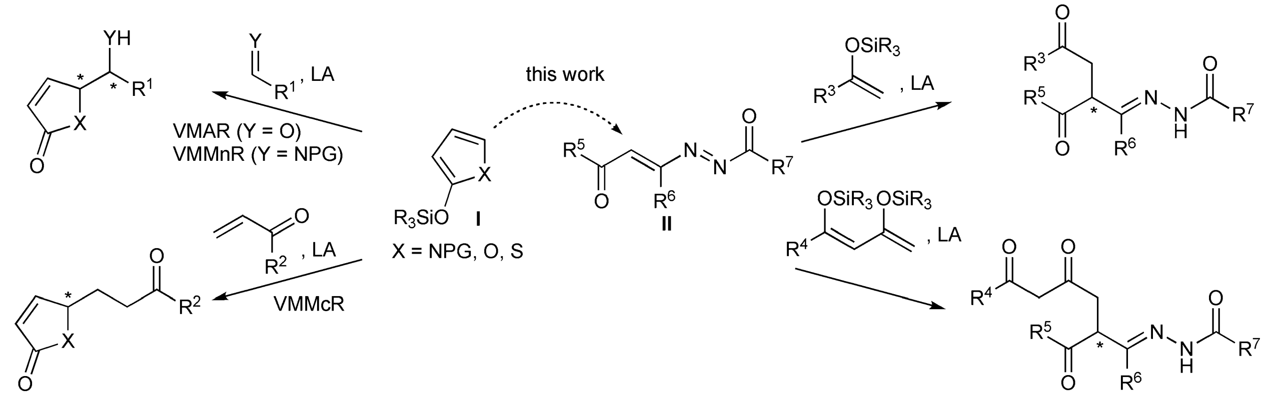
The past two decades have witnessed a blossom of research articles among the organic chemistry assembly where the bulk of reactions which were historically carried out in organic solvents have been revisited in an aqueous environment, be it as the sole reaction medium, be it in the presence of accompanying co-solvents or excess solubilizing organic reactants.[1]

The ever increasing awareness of the utility of water in organic synthesis is rooted on diverse, key contributions, which include the seminal investigations by Breslow and co-workers[2] who first reported quantitative studies on the effect of water as a rate- and selectivity-enhancing medium in Diels–Alder cycloaddition reactions in dilute homogeneous solutions. Practical and semantic stigmatization on this subject matter was then offered by Sharpless and colleagues[3] who showed how chemical reactions carried out on-water – that is under strictly aqueous, heterogeneous conditions on a preparative scale – could benefit from marked advantages in terms of synthetic efficiency, stereochemical control, and overall practicality as well.

Furthermore, an evermore ecological perception of chemical transformations, which tend to emulate the ideal reaction conditions of biochemical processes within the living organisms, has fuelled such a general interest toward aqueous-based organic reactions.

Lastly, a couple of additional key points contribute to support the "resurgence" of aqueous media in organic synthesis, i.e., (i) the introduction of novel water-tolerant reactants and catalytic systems in the organic synthesis palette,[4] and (ii) the skillful intervention of talented theoreticians who furnished (and still are furnishing) a robust background of thermodynamic, kinetic, and computational studies to support and rationalize results in this often cryptic field.[5]

Among the classical organic reactions which have been revisited under an aqueous perspective, the Mukaiyama–Michael addition reaction[6] – that is the



Scheme 1. Exploiting the d$_4$ reactivity of 2-silyloxyheterocycles **I** (*left*) and the a$_4$ reactivity of 1,2-diaza-1,3-dienes **II** (*right*). (LA = Lewis acid; VMAR = vinylogous Mukaiyama aldol reaction; VMMnR = vinylogous Mukaiyama–Mannich reaction; VMMcR = vinylogous Mukaiyama–Michael reaction).

Lewis acid-promoted conjugate addition of silyl enol ether (or silyl ketene acetal) donors to α,β-unsaturated carbonyl acceptors – has received only scant attention,[7,8] possibly because of the inherent lability of both silyl enolates and common Lewis acid promoters towards hydrolysis. Accounts on the use of water in the vinylogous version of the Mukaiyama–Michael reaction, which deploys vinylogous silyl enolate donors,[9] have not been reported so far.

During ongoing studies in the field of vinylogous Mukaiyama-type aldol, Mannich, and Michael additions, we came to appreciate the virtues of diverse heterocyclic 2-silyloxydienes of type **I** (Scheme 1, *left*) which may act as useful d$_4$ reactants in coupling additions to carbonyl compounds, aldimines, or electron-deficient alkenes.[9]

Typically, these reactions were performed in the presence of stoichiometric amounts of Lewis acid promoters in CH_2Cl_2 or Et_2O as solvent.[10] On the other hand, long-standing experience matured in the use of 1,2-diaza-1,3-dienes[11] of type **II** as precious a$_4$ synthons in a multitude of Michael-type addition reactions including Mukaiyama–Michael-type process[11a,b] (Scheme 1, *right*), has prompted us to investigate the behaviour of these substrates with diverse heterocyclic 2-silyloxydienes. In general, the Mukaiyama version of the Michael reaction of silyl enol ethers was performed under the agency of catalytic amounts of Lewis acid activators in organic solvents to furnish 1,4-hydrazonic adduct intermediates eventually leading to the nitrogen-containing heterocyclic target compounds.[11a,b,12]

Herein, the ability of heterocyclic 2-silyloxydienes to couple to 1,2-diaza-1,3-dienes according to a vinylogous Mukaiyama–Michael reaction (VMMcR) modality under both a traditional organic environment and in an aqueous medium is assayed and compared. Exploitation of the emerging vinylogous Michael adducts in *all-on-water* one-pot procedures is also discussed, leading to functionality-rich pyrrole-carboxylates in good yields and outstanding practicality.

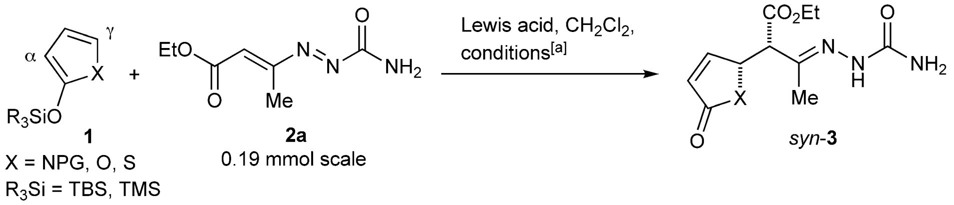
We began our studies with the model reaction between *N-tert*-butoxycarbonyl-2-[(*tert*-butyldimethyl)silyloxy]pyrrole (**1a**) and ethoxycarbonyl-substituted diazadiene **2a**, which was screened with conventional Lewis acid promoters in CH_2Cl_2 (Table 1). Using $BF_3{\cdot}OEt_2$ in both stoichiometric and catalytic quantities at −78 °C produced very poor results (not shown),[13] while catalytic amounts of the same Lewis acid at 25 °C ensured good levels of conversion to the expected Michael adduct **3a**, which was recovered as a separable 70:30 *syn:anti* diastereomeric mixture (entry 1).

Similar conversions and reaction rates were observed with other Lewis acid catalysts, albeit with *syn:anti* stereoselectivities varying from fairly good to poor. Significantly, the presence of the Lewis acid component turned out to be essential, since the reaction between the sole **1a** and **2a** in CH_2Cl_2 gave no detectable amounts of product (entry 3). Variation of the donor reactant was also scrutinized. Change of the TBS for a TMS group in the pyrrole **1** resulted in a significant rate acceleration of the reaction (3 h *vs.* 6 h, entry 4 *vs.* 2), while both efficiency and stereoselectivity remained almost untouched.

By deployment of commercial 2-(trimethylsilyloxy)-furan (**1c**), the coupling reaction to **2a** in the presence of various Lewis acid catalysts occurred with equally complete γ-regioselection, affording the corresponding butenolide product **3b** in satisfactory yields albeit with very modest diastereoselection (e.g., entry 5). As an exception, the $Sc(OTf)_3$-catalyzed reaction involving thiophene-derived silyl ether **1d** was unsuccessful, possibly because of the rapid degradation of the labile thiobutenolide vinylogous Michael product under these reaction conditions (entry 6).

The relative configuration of the major pyrrolinone product *syn*-**3a** was unambiguously certified by single

Table 1. Screening conditions for organic-phase VMMcR using heterocyclic silyloxydienes **1** and 1,2-diaza-1,3-diene **2a**.



Entry	Donor	R_3Si	X	Lewis acid (mol%)	Product[b]	Conversion [%][c]	γ:α[c]	*dr* (*syn:anti*)[c,d]
1	**1a**	TBS	NBoc	$BF_3·OEt_2$ (10)	**3a**	80	>99:1	70:30
2	**1a**	TBS	NBoc	$Sc(OTf)_3$ (10)	**3a**	92	>99:1	78:22
3	**1a**	TBS	NBoc	–	–	–	–	–
4[e]	**1b**	TMS	NBoc	$Sc(OTf)_3$ (10)	**3a**	96	>99:1	78:22
5	**1c**	TMS	O	$Sc(OTf)_3$ (10)	**3b**	72	>99:1	67:33
6	**1d**	TMS	S	$Sc(OTf)_3$ (10)	–[f]	–	–	–
7[g]	**1b**	TMS	NBoc	$Sc(OTf)_3$ (10)	**3a**	85	>99:1	77:23

[a] Unless otherwise noted, reactions were performed with silyloxydiene **1**/1,2-diaza-1,3-diene **2a** (1.15/1.00 mol equiv.), Lewis acid (mol%), with a substrate concentration of 0.06 M (0.19 mmol scale) in dry CH_2Cl_2, at 25 °C under an argon atmosphere, with a 6 h reaction time. For details, see Supporting Information.

[b] Racemic *syn/anti* product.

[c] Determined by ^1H NMR analysis of the crude reaction product.

[d] Relative configuration of **3a** certified by X-ray analysis of *syn*-**4a** (see text for details).

[e] Reaction time 3 h.

[f] Degradation products detected.

[g] Substrate concentration of 0.14 M (0.7 mmol scale); reaction time 48 h.

crystal X-ray analysis of its saturated counterpart, namely compound *syn*-**4a**, as illustrated in Figure 1. At this point, in recognizing the feasibility of the VMMcR between heterocyclic silyloxydienes and 1,2-diaza-1,3-dienes under conventional organic routes, we next wondered whether this valuable carbon-carbon bond-forming reaction could be further dignified by the use of viable aqueous procedures.

At first we screened conditions for the model reaction between the highly reactive TMS-protected pyrrole **1b** and 1,2-diaza-1,3-diene **2a**, on a 0.7 mmol preparative scale in 0.14 M solutions. We soon realized that the presence of water either as the sole reaction medium or in the co-presence of other polar solvents or salts could expedite the reaction rates up to 20 times as compared to the full organic counterparts (*cf.* entry 7 in Table 1), producing the expected VMMcR products in high yields and selectivities (Table 2). Significant rate increases (by 9 to 24 times, entries 3 and 5 *vs.* 11) were observed over reactions

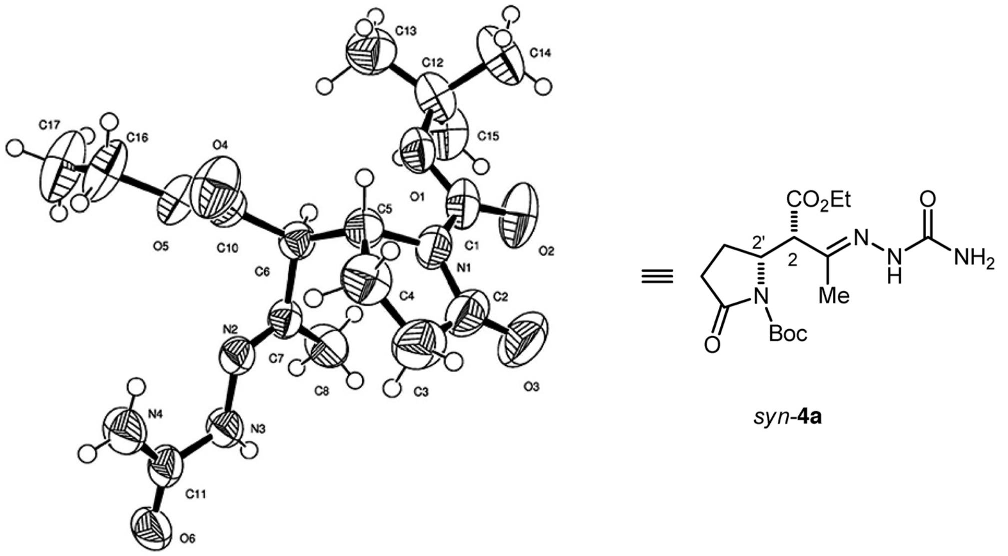
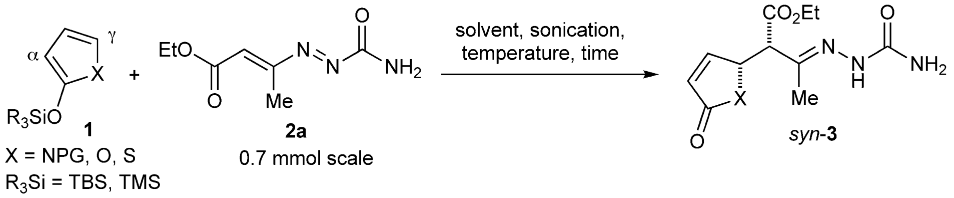


Figure 1. ORTEP representation of the X-ray structure of racemic derivative *syn*-**4a**; the (2*S*,2′*R*)-enantiomer is shown.

Table 2. Screening conditions for aqueous, open-air VMMcR using heterocyclic silyloxydienes **1** and 1,2-diaza-1,3-diene **2a**.[a]



Entry	Donor	R_3Si	X	Solvent	Temp. [°C]	Time [h]	Product[b]	Yield [%][c]	γ:α[d]	*dr* (*syn:anti*)[d,e]
1[f,g]	**1b**	TMS	NBoc	H_2O/MeOH (1:1)	25	24	**3a**	45	>99:1	89:11
2[f]	**1b**	TMS	NBoc	H_2O/MeOH (1:1)	38–40	8	**3a**	95	>99:1	80:20
3	**1b**	TMS	NBoc	H_2O/MeOH (1:1)	38–40	8	**3a**	90	>99:1	80:20
4	**1b**	TMS	NBoc	H_2O/*t*-BuOH (1:1)	38–40	48	**3a**	75	>99:1	56:45
5	**1b**	TMS	NBoc	H_2O	38–40	3	**3a**	96	>99:1	80:20
6	**1a**	TBS	NBoc	H_2O	38–40	3.5	**3a**	82	>99:1	>99:1
7[g]	**1b**	TMS	NBoc	H_2O	25	24	**3a**	97.5	>99:1	80:20
8	**1b**	TMS	NBoc	brine	38–40	2.5	**3a**	90	>99:1	>99:1
9	**1c**	TMS	O	H_2O	38–40	2	**3b**	53	>99:1	>99:1
10	**1d**	TMS	S	H_2O	38–40	1.5	**3c**	87	>99:1	63:37
11	**1b**	TMS	NBoc	neat	38–40	72	**3a**	55	>99:1	77:23

[a] Unless otherwise noted, reactions were performed with silyloxydiene **1**/1,2-diaza-1,3-diene **2a** (1.15/1.00 mol equiv.), with a substrate concentration of 0.14 M (0.7 mmol scale) in the indicated solvent, in air, at atmospheric pressure under sonication (59 KHz). For details, see Experimental Section.

[b] Racemic *syn/anti* product.

[c] Combined isolated yield.

[d] Determined by ^{1}H NMR analysis of the crude reaction product.

[e] Relative configuration of **3a** certified by X-ray analysis of *syn*-**4a** (see text for details).

[f] Carried out in the presence of $Sc(OTf)_3$ (10 mol%).

[g] Carried out under vigorous stirring without sonication.

carried out in the absence of any solvent, indicating that rate acceleration could not be ascribed to the sole increasing concentration effect.

The presence of catalytic, water-tolerant Lewis acids [for example, $Sc(OTf)_3$] turned out to be superfluous, since its depletion did not compromise the effectiveness of the transformation (entries 1 and 2 *vs.* 3-8). Conducting the reaction under ultrasonic irradiation, on the other hand, did produce significantly enhanced reaction rates by 3 to 8 times (entries 1 *vs.* 2 and 5 *vs.* 7).

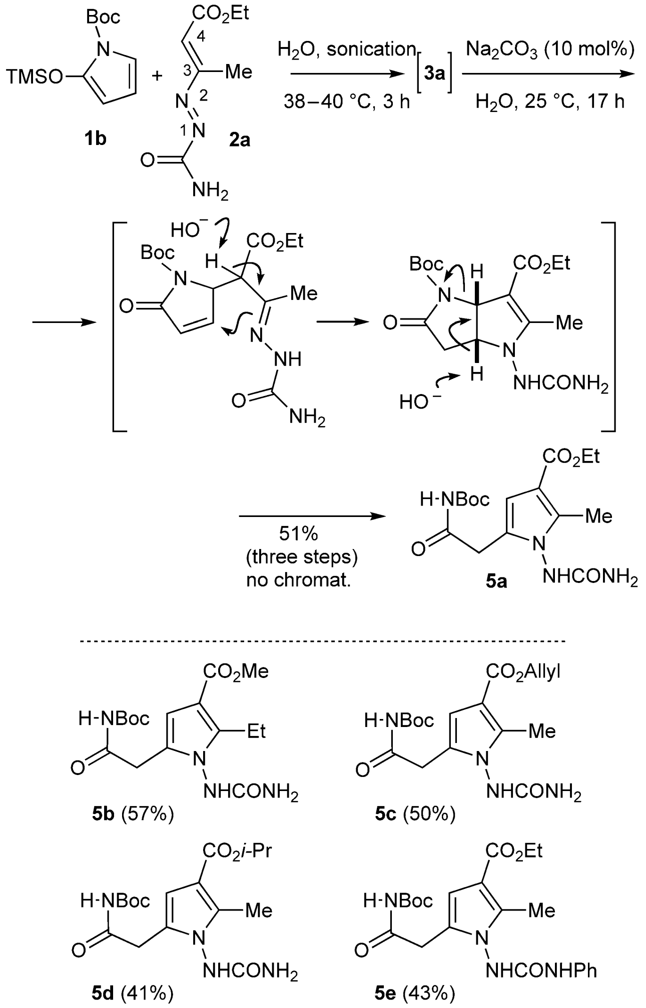
Using an H_2O/MeOH (1:1) solvent mixture, reactants **1b** and **2a** completely dissolved in the reaction medium and afforded the vinylogous Michael product **3a** in high yields, with exclusive γ-site selectivity and 80:20 *syn:anti dr* (entry 3). On the other hand, by adding liquid pyrrole **1b** and solid 1,2-diaza-1,3-diene **2a** sequentially in an open-air water medium under 59 KHz sonication at 38–40 °C (entry 5), a heterogeneous suspension of finely dispersed reactants formed, with concomitant color turning from dark-red to pale-yellow. After 3 h, precipitation of a yellowish solid decretes the reaction conclusion.[14] Compound **3a** is recovered in >99% conversion by simple filtration and extraction as an 80:20 *syn:anti* diastereomeric mixture.

To access diastereomerically pure *syn*-**3a**, the reaction may be performed utilizing either TBS-protected pyrrole **1a** in pure water (entry 6) or pyrrole **1b** in brine (entry 8). However, both reactions suffer from slightly diminished yields and scant practicality.[15]

Noticeably, this on-water procedure could be conveniently extended to oxygen- and sulphur-containing nucleophiles (entries 9 and 10); both reactions proceeded speedly (2 h and 1.5 h), with clean recovery of the corresponding butenolide-type products **3b** and **3c** in acceptable-to-good yields and diastereomeric ratios.[16]

To demonstrate the synthetic potential of the disclosed on-water procedure, a one-pot methodology was assayed which involved addition of catalytic aqueous carbonate solution to the open-air reaction vessel at ambient temperature once the conversion of the starting reactants **1b** and **2a** to **3a** was judged complete (Scheme 2). After 17 h, water-insoluble pyrrole **5a** formed, which could be isolated as a pure solid in 51% overall yield by simple filtration.

Mechanistically, we surmised[17] that, after the initial formation of the Michael adduct **3a**, the added base triggers a cascade of events featuring an intramolecular aza-Michael reaction to furnish a diazabicyclo[3.3.0] intermediate, which is promptly subjected to ring opening and aromatization to pyrrole **5a**.



Scheme 2. Profiling the scope of the VMMcR on water (isolated yields for the one-pot three-step procedure from the corresponding 1,2-diaza-1,3-diene, in parenthesis).

Pyrroles of type **5a** are functionally dense heterocycles from which several diverse products may, in principle, be generated. For instance, oxidative or reductive N−N cleavage[18] may furnish nitrogen-free pyrrole-carboxylates, while saturation of the pyrrole carbon-carbon double bonds may lead to unusual yet intriguing homoproline β-amino acid privileged structures.

On the basis of these results, we were able to extend the one-pot three-step protocol to variously substituted azo-ene substrates. As shown in Scheme 2, a panel of variously adorned pyrrole-carboxylates **5b–e** was easily accessed in overall yields ranging from 41 to 57% from the respective 1,2-diaza-1,3-dienes **2b–e**, with no need for any chromatographic intervention.

This transformation proved sensitive to the nature of the substituents at the N-1 and C-4 positions of the starting 1,2-diaza-1,3-diene reactant. As a rule, no reaction took place either when the carbamoyl group at N-1 was replaced by a phenylamino function, or the ester moiety at C-4 was substituted by an amide group; and this is possibly due to a LUMO rise of the azadiene C-4 carbon atom.

As for the dramatic role exerted by water in this transformation, we assume that concurrent on-water and in-water phenomena may occur and multiple factors may simultaneously operate, which involve hydrophobic effects, trans-phase H-bonding, and solvent polarity effects. Specifically, for those reactions carried out under heterogeneous conditions, one or more water molecules at the boundary between the substrate particles and water are speculated to activate the reactants and strictly control their mutual position in the transition states.[1e–h,5c–e]

In conclusion, we have described highly practical and efficient methods that allow for the direct construction of varied heteroatom-carrying hydrocarbon skeletons. In particular, the first vinylogous Mukaiyama–Michael addition reaction has been reported, where heterocyclic 2-silyloxydienes and 1,2-diaza-1,3-dienes are coupled on-water in open-air vessels under ultrasound irradiation at 38–40 °C. The butenolide-type Michael products obtained (compounds **3**) are either easily isolated, or may they be involved in a base-triggered, *all-in-water* reaction cascade ultimately resulting in production of differently adorned pyrrole-carboxylates. This one-pot, three-step procedure can come very close to ideal green conditions[19] since it condenses optimal requisites such as efficiency, atom economy, safety, reaction speed, preparative usefulness, and easy of product isolation.

Instructive is also the direct comparison between the on-water VMMcR procedure and the "organic" counterpart carried out using conventional Lewis acid promoters and organic solvents; the superior role of water in terms of reaction rate, stereoselectivity, efficiency and general applicability has been widely demonstrated.

Finally, while the interpretation of the actual role exerted by water during these processes remains largely speculative, this study may furnish a further piece in unravelling the fundamental actions that govern the on-water catalysis at the molecular level.

Experimental Section

On-Water One-Pot Three-Step Synthesis of Pyrroles 5a-e. Preparation of Ethyl 5-[(*tert*-butoxycarbonylcarbamoyl)methyl]-2-methyl-1-ureido-1*H*-pyrrole-3-carboxylate (5a)

To a suspension of 1,2-diaza-1,3-diene (**2a**) (130 mg, 0.7 mmol) in water (5 mL) under sonication at 38–40 °C in an open-air vessel, pyrrole **1b** (206 mg, 0.81 mmol) was added. After 1 h the solution turned from red to orange, and to a pale yellow color after 3 h reaction. At this point the reaction was monitored by TLC (EtOAc/MeOH 98:2) to check the complete disappearance of 1,2-diaza-1,3-diene **2a**. Sodium carbonate (7.4 mg, 0.07 mmol) was then added, the reaction vessel was removed from the ultrasound bath and the solution was kept under magnetic stirring for 17 h at room temperature. Filtration of the reaction mixture gave the pure pyrrole-carboxylate **5a** as a white solid without need of further purification; yield: 131.5 mg (51% yield for three steps from **2a**); mp 141 °C. IR (KBr): $\nu = 3454$, 3342, 2956, 2924, 2853, 1771, 1683, 1258, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.40$ (bs, 1H, NH), 8.06 (s, 1H, NH), 6.43 (s, 1H, H-4), 4.88 (bs, 2H, NH_2), 4.25 (q, $J = 7.1$ Hz, 2H, $CH_3\mathit{CH_2}O$), 4.17 (d, $J = 18.0$ Hz, 1H, H-1′a), 3.85 (d, $J = 18.0$ Hz, 1H, H-1′b), 2.46 (s, 3H, CH_3), 1.50 (s, 9H, *t*-Bu), 1.31 (t, $J = 7.1$ Hz, 3H, $\mathit{CH_3}CH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.2$ (Cq, C-2′), 165.0 (Cq, $\mathit{C}O_2Et$), 158.4 (Cq, $\mathit{C}ONH_2$), 151.0 (Cq, Boc), 137.7 (Cq, C-2), 124.9 (Cq, C-5), 111.2 (Cq, C-3), 109.1 (CH, C-4), 83.5 (Cq, *t*-Bu), 59.9 (CH_2, $CH_3\mathit{CH_2}O$), 33.9 (CH_2, C-1′), 28.2 (3C, CH_3, *t*-Bu), 14.7 (CH_3, $\mathit{CH_3}CH_2O$), 10.8 (CH_3, Me); R_f 0.18 (8:2 acetone/hexane); MS (ESI$^+$): $m/z = 291.3$ $[M-Boc+Na]^+$; 391.2 $[M+Na]^+$; anal. calcd. for $C_{16}H_{24}N_4O_6$ (368.38): C 52.17, H 6.57, N 15.21; found: C 52.23, H 6.60, N 15.15.

Supporting Information

Description of experimental procedures, characterization data, crystal data for compound *syn*-**4a**, and selected NMR spectra are available as Supporting Information.

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[15] Under the conditions of entry 8 (Table 2), in particular, extensive molecular aggregation rendered separation and further manipulation of the adduct formed somewhat troublesome.

[16] The 2,2′-stereodisposition of the predominating butenolide **3b** and thiobutenolide **3c** could not be attributed with certainty.

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