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Straightforward Access to Pyrazines, Piperazinones, and Quinoxalines by Reactions of 1,2-Diaza-1,3-butadienes with 1,2-Diamines under Solution, Solvent-Free, or Solid-Phase Conditions

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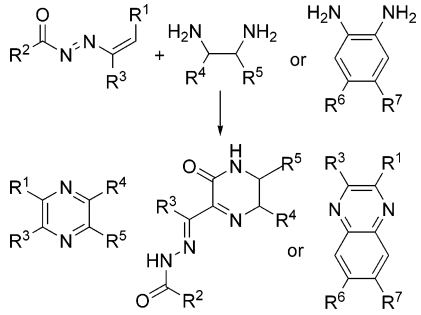

The preparation of tetrahydropyrazines, dihydropyrazines, pyrazines, piperazinones, and quinoxalines by 1,4-addition of 1,2-diamines to 1,2-diaza-1,3-butadienes bearing carboxylate, carboxamide, or phosphorylated groups at the terminal carbon and subsequent internal heterocyclization is described. The solvent-free reaction of carboxylated 1,2-diaza-1,3-butadienes with the same reagents affords piperazinones, while phosphorylated 1,2-diaza-1,3-butadienes yield phosphorylated pyrazines. The solid-phase reaction of polymer-bound 1,2-diaza-1,3-butadienes with 1,2-diamines produces pyrazines.

Introduction

Pyrazines[1,2] and quinoxalines[3,4] are widely used intermediates in medicinal chemistry. Furthermore, quinoxalines constitute the skeleton of natural products and antibiotics,[5] while pyrazines, which are biosynthesized from amino acids, are common units in a wide variety of marine natural products showing cytostatic

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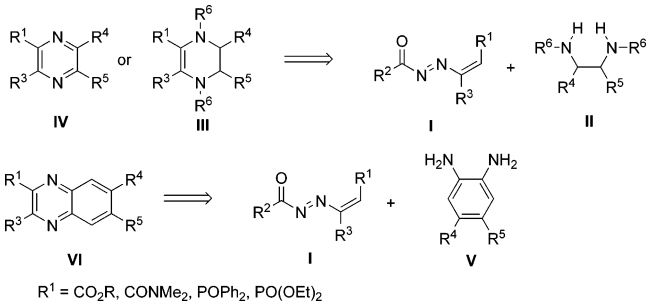
SCHEME 1



and antitumor properties,[6] and pyrazinamides[7] as well as pyrazinesters[8] have been successfully evaluated in vitro and in vivo for antituberculosis activity. Therefore, the development of new methods for synthesis of pyrazine and quinoxaline derivatives acquired relevance in recent years.

In a preliminary paper,[9] carboxylated 1,2-diaza-1,3-butadienes[10,11] (**I**, $R^1 = CO_2R$) have been used for the preparation of pyrazinesters (**IV**, $R^1 = CO_2R$) (Scheme 1) and interesting piperazinones,[12] while phosphorylated 1,2-diaza-1,3-butadienes (**I**, $R^1 = POR_2$) have been used for the preparation of α-aminophosphonates[13] and pyridazines.[14] Here, we report the synthesis of different pyrazine esters and new pyrazinamides, pyrazinephosphine oxides, and pyrazinephosphonates. We also describe an efficient strategy for the preparation of unknown functionalized tetrahydropyrazines[15] **III** derived from α-amino acid ($R^1 = CO_2R$ or $R^1 = CONMe_2$) and new quinoxalines **VI** (Scheme 1) derived from α-aminophosphorus mimetic compounds ($R^1 = POR_2$). Since in recent years combinatorial synthesis of small organic molecules has received much attention,[16,17] we have reported in previous papers the construction of 1,2-diaza-1,3-butadienes bounded to polystyrene resins[18,19a] or poly(ethylene glycol).[20] In this work, we also investigated the use of polymer-bound 1,2-diaza-1,3-butadienes as building blocks for the facile solid-phase preparation of pyrazine derivatives.

Results and Discussion

The synthesis of carboxylate, carboxamide, phosphine oxide, and phosphonate pyrazines **9** from 1,2-diaza-1,3-butadienes **1a**−**g** and (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine **2a**, (±)-*trans*-**2b**, or (±)-*cis*-1,2-diaminocyclohexane **2c** is shown in Schemes 2 and 3 and Table 1. 1,2-Diaza-1,3-butadienes **1a**−**e** reacted in acetonitrile at room temperature with diamine compound **2a** producing dihydropyrazines **6a**−**c** (Scheme 2, path a, Table 1). Under the same conditions, compounds **1b**−**e** reacted with **2b** affording dihydropyrazines **6d**−**f** (Scheme 2, path a, Table 1). The reaction takes place by preliminary nucleophilic attack of an amino group of 1,2-diamines **2** at the terminal carbon of the heterodiene system **1** to give the 1,4-adduct (Michael type) **3** that promptly affords piperazine **4** by subsequent internal nucleophilic attack of the remaining amino group at the carbon of the hydrazono moiety. Spontaneous elimination of the hydrazine residue leads to substituted 1,4,5,6-tetrahydropyrazines **5** isolable by fast purification with flash chromatography only in the case of the reaction between **1b** and **2a**. This product was identified as ethyl (5*R*,6*R*)-3-methyl-5,6-diphenyl-1,4,5,6-tetrahydro-2-pyrazinecarboxylate **5a** by ^{1}H NMR spectroscopy. In the other cases, spontaneous oxidation of **5** gave rise directly to the corresponding 2-carboxylate or 2-carboxamide 5,6-dihydropyrazines **6a**−**f**. 2-Carboxylate or 2-carboxamide pyrazines **9a**−**c**,**f**−**h** were obtained from pure products **6** or reaction mixtures by aromatization with phenyltrimethylammonium tribromide (PTAB) for compounds **9a**,**b** and **9f**−**h** or by treatment with trifluoroacetic acid in acetonitrile

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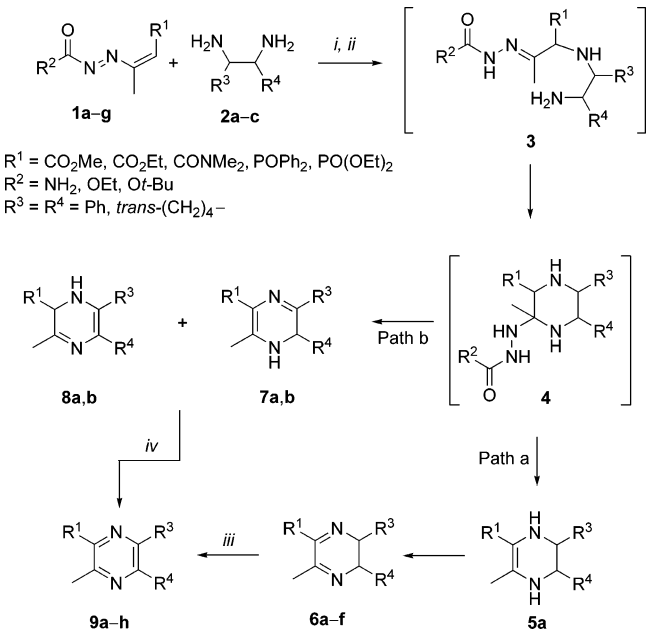
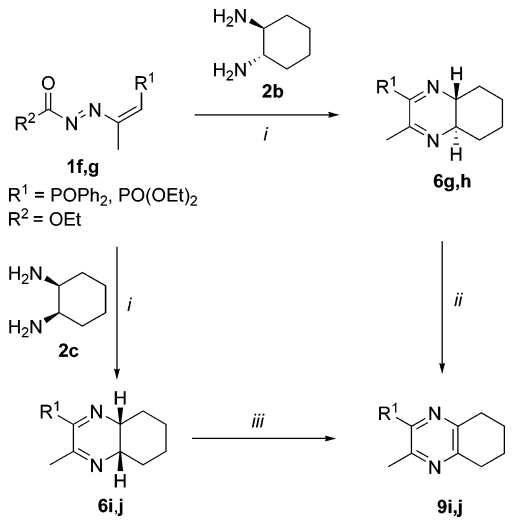
SCHEME 2[a]



[a] Reagents and conditions: (i) for **1a**−**e** + **2a** and **1b**−**e** + **2b**, MeCN, rt (path a); (ii) for **1f,g** + **2a**, CH_2Cl_2, rt (Path b); (iii) for **6a**,**b**,**d**−**f**, PTAB, CH_2Cl_2, rt, for **6c**, CF_3COOH, MeCN, reflux; (iv) *p*-benzoquinone, dioxane, reflux.

SCHEME 3[a]



[a] Reagents and conditions: (i) CH_2Cl_2, rt; (ii) *p*-benzoquinone, dioxane, reflux; (iii) CH_2Cl_2, rt.

under reflux for compound **9c** (Scheme 2, path a, Table 1). Similarly, the synthesis of pyrazine derivatives containing phosphine oxide or phosphonate groups was achieved by reaction of 1,2-diaza-1,3-butadienes **1f**,**g**[21] with 1,2-diphenyl-1,2-ethanediamine **2a**. In the case of **1f**, the reaction at room temperature led to substituted 4,5-dihydropyrazinephosphine oxide **7a** (Scheme 2, path b), while in the case of 1,2-diaza-1,3-butadiene **1g**, the reaction gave a mixture of isomeric substituted 4,5- (**7b**) and 1,2-dihydropyrazine **8b** (Scheme 2, path b). These dihydropyrazines were characterized by ^{31}P NMR spectra, **7b** showing one absorption at δ_P 18.3 ppm, while absorption at δ_P 14.8 ppm was observed for dihydropyrazine **8b**. Likewise, the ^1H NMR spectra of **7b** gave a well resolved doublet for *H*-5 at δ_H 5.67 ppm ($^5J_{PH}$ = 4.0 Hz), while **8b** gave a well resolved doublet at δ_H 4.90 ppm ($^2J_{PH}$ = 23.7 Hz) for *H*-2. The oxidation of 1,2-dihydropyrazine **7a** with *p*-benzoquinone in dioxane under reflux led to the formation of pyrazinephosphine oxide **9d** (Scheme 2, path b, Table 1), while the aromatization of the mixture of isomeric dihydropyrazines **7b** and **8b** can be performed under the same conditions producing pyrazinephosphonate **9e** (Scheme 2, path b, Table 1). Therefore, this strategy affords an easy and efficient entry to phosphorylated pyrazines. It is known that phosphorus substituents regulate important biological functions,[22] and the introduction of organophosphorus functionalities in simple synthons may afford the development of new strategies for the preparation of phosphorus substituted compounds.[23] However, pyrazines directly substituted with phosphorus-containing functional groups have received scarce attention, probably due to the lack of methods of synthesis of these substrates. Only recently, the first synthesis of phosphorylated analogues of pyrazinamides such as substituted pyrazines containing either one phosphorylated group at 2-position[24] or two phosphonate groups at the 2,5-positions[24,25] was reported.

Michael addition of (±)-*trans*-1,2-diaminocyclohexane **2b** to the heterodiene system of 1,2-diaza-1,3-butadiene **1f** in methylene chloride at room temperature gave rise stereoselectively to the formation of *trans*-2,3-dihydropyrazine-5-phosphine oxide **6g** in 94% yield (Scheme 3, Table 1). In fact, the compound **6g** resulted only *trans*-isomer by NMR spectroscopy. The reaction of 1,2-diaza-1,3-butadiene **1g** with (±)-*trans*-1,2-diaminocyclohexane **2b** provided dihydropyrazine **6h** in good yield (Scheme 3, Table 1). Aromatization of dihydropyrazine **6g** was performed by oxidation with *p*-benzoquinone in dioxane under reflux producing pyrazinephosphine oxide **9i** (Scheme 3, Table 1). Unfortunately, the oxidation of dihydropyrazine **6h** under the same conditions did not lead to 2-phosphonylpyrazine **9**, but only to decomposition products. The stereoselectivity of the process for the preparation of 2-phosphorylated dihydropyrazines **6** was also studied. For this reason, the reaction of 1,2-diaza-1,3-butadienes **1f**,**g** with (±)-*cis*-1,2-diaminocyclohexane **2c** was explored giving rise to *cis*-dihydropyrazines **6i**,**j** (Scheme 3, Table 1). In this case, the oxidation readily occurred in the reaction media (air atmosphere), and pyrazine **9i** was easily obtained from dihydropyrazine **6i** (Table 1). However, pyrazine **9j** was not possible to isolate, but its presence in the reaction mixture was confirmed by ^1H and ^{31}P NMR together with the dihydropyrazine **6j** (Scheme 3, Table 1).

Pyrazine-2-carboxylate **9k** has been directly obtained by reaction of 1,2-diaza-1,3-butadienes **1a**,**b** in ethanol with 1,2-ethanediamine **2d**. The reaction was allowed to stand at room temperature until the complete disappearance of the reagents and then refluxed in the presence of palladium on carbon

(21) These aza-alkenes **1f**,**g** are prepared "in situ" by HCl elimination of α-chlorohydrazones through base treatment.[13]

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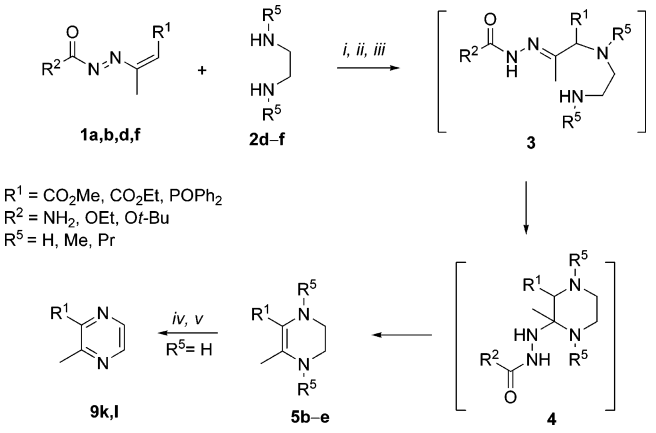
TABLE 1. Yields of 1,4,5,6-Tetrahydropyrazines 5b−e, 5,6-Dihydropyrazines 6a−j, and Pyrazines 9a−l

1	R^1	R^2	2	R^3	R^4	R^5	5	yield[a] (%)	6	yield[a] (%)	9	yield[a] (%)	yield[b] (%)
1a	CO_2Et	O*t*-Bu	**2a**	Ph	Ph				**6a**	66	**9a**	60	86
1b	CO_2Et	NH_2	**2a**	Ph	Ph		**5a**		**6a**	62	**9a**	56	87
1c	CO_2Me	NH_2	**2a**	Ph	Ph				**6b**	68	**9b**	62	86
1d	CO_2Me	O*t*-Bu	**2a**	Ph	Ph				**6b**	61	**9b**	58	91
1e	$CONMe_2$	NH_2	**2a**	Ph	Ph				**6c**	52	**9c**	40	
1f	$POPh_2$	OEt	**2a**	Ph	Ph						**9d**	92	
1g	$PO(OEt)_2$	OEt	**2a**	Ph	Ph						**9e**	70	
1b	CO_2Et	NH_2	**2b**	*trans*-$(CH_2)_4$−					**6d**	51	**9f**	36	73
1c	CO_2Me	NH_2	**2b**	*trans*-$(CH_2)_4$−					**6e**	49	**9g**	46	90
1d	CO_2Me	O*t*-Bu	**2b**	*trans*-$(CH_2)_4$−					**6e**	45	**9g**	43	93
1e	$CONMe_2$	NH_2	**2b**	*trans*-$(CH_2)_4$−					**6f**	60	**9h**	13	41
1f	$POPh_2$	OEt	**2b**	*trans*-$(CH_2)_4$−					**6g**	94	**9i**	67	
1g	$PO(OEt)_2$	OEt	**2b**	*trans*-$(CH_2)_4$−					**6h**	82			
1f	$POPh_2$	OEt	**2c**	*cis*-$(CH_2)_4$−					**6i**	*c,d*	**9i**	*e*	
1g	$PO(OEt)_2$	OEt	**2c**	*cis*-$(CH_2)_4$−					**6j**	*f*	**9j**	*g,e*	
1a	CO_2Et	O*t*-Bu	**2d**	H	H	H					**9k**	32	
1b	CO_2Et	NH_2	**2d**	H	H	H					**9k**	35	
1f	$POPh_2$	OEt	**2d**	H	H	H					**9l**	90	
1a	CO_2Et	O-*t*-Bu	**2e**	H	H	Me	**5b**	58					
1d	CO_2Me	O-*t*-Bu	**2e**	H	H	Me	**5c**	56					
1a	CO_2Et	O-*t*-Bu	**2f**	H	H	Pr	**5d**	75					
1d	CO_2Me	O-*t*-Bu	**2f**	H	H	Pr	**5e**	71					

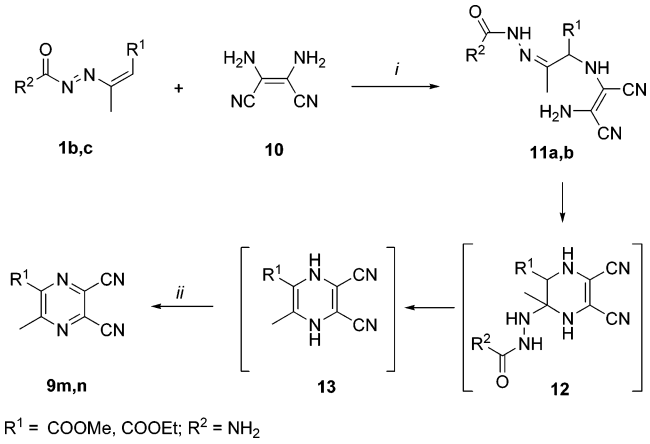
[a] Yields of pure products are based on 1,2-diaza-1,3-butadienes **1a**−**g**. [b] Yields of pure products are based on reagent **6**. [c] Oxidation of dihydropyrazine **6i** readily occurred, and pyrazine **9i** was directly obtained. [d] This oxidation occurred at room temperature in the presence of air atmosphere. [e] Pyrazines **9i** and **9j** were obtained in near quantitative yield. [f] A mixture of dihydropyrazine **6j** and pyrazine **9j** was obtained after purification of the crude compound **6j** in a ratio of 3.7/1. [g] Pyrazine **9j** was not isolable, but its presence was confirmed by ^1H and ^{31}P NMR together with the dihydropyrazine **6j**.

SCHEME 4[a]



[a] Reagents and conditions: (i) for **1a**,**b** + **2d**, EtOH, rt; (ii) for **1a**,**d** + **2e**,**f**, MeCN, rt; (iii) for **1f** + **2d**, CH_2Cl_2, rt; (iv) for **1a,b** + **2d**, Pd/C, EtOH, reflux; (v) for **1f** + **2d**, *p*-benzoquinone, dioxane, reflux.

SCHEME 5[a]



[a] Reagents and conditions: (i) MeCN, rt; (ii) MeCN, CF_3COOH, reflux.

TABLE 2. Yields of Hydrazones 11a,b and 5,6-Dicyano-3-methyl-2-pyrazinecarboxylates 9m,n

1	R^1	R^2	11	yield[a] (%)	9	yield[a] (%)	yield[b] (%)
1b	CO_2Et	NH_2	**11a**	62	**9m**	58	78
1c	CO_2Me	NH_2	**11b**	55	**9n**	74	87

[a] Yields of pure products are based on 1,2-diaza-1,3-butadienes **1b**,**c**. [b] Yields of pure products are based on reagent **11**.

(Pd/C)[26] (Scheme 4, Table 1). In a similar way, 1,2-diaza-1,3-butadiene **1f** reacted with 1,2-diaminoethane **2d** in methylene chloride at room temperature to give pyrazinephosphine oxide **9l** in excellent yield by treatment of the reaction mixture with *p*-benzoquinone in dioxane under reflux (Scheme 4, Table 1). Unfortunately, all attempts to obtain dihydropyrazines **6a**−**j** and pyrazines **9a**−**l** in good yields with the same procedure failed likely because of the different substituents. For this reason, we used the most suitable reaction conditions depending on the nature of the substrate. To improve the scope of this synthetic methodology, the reaction of *N*,*N*′-dimethylethylenediamine **2e** and *N*,*N*′-di-*n*-propylethylenediamine **2f** with 1,2-diaza-1,3-butadienes **1a**,**d** in acetonitrile at room temperature was performed (Scheme 4). In these cases, the presence of alkyl groups on both nitrogen atoms of diamine compounds **2e**,**f** prevents the final oxidation process giving new 1,4,5,6-tetrahydropyrazine-2-carboxylates **5b**−**e** in good yields (Scheme 4, Table 1).

The reaction of diaminomaleonitrile **10** with 1,2-diaza-1,3-butadienes **1b**,**c** in acetonitrile at room temperature was also investigated (Scheme 5). The nucleophilic attack of amino group of compound **10** at the terminal carbon of the heterodiene system of 1,2-diaza-1,3-butadienes **1b**,**c** led to hydrazone 1,4-adducts **11a**,**b** isolated by chromatography on silica (Scheme 5, Table

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TABLE 3. Solvent-Free Synthesis of Hydrazones 3a−d, Pyrazines-2-phosphorylates 9d,e,i, Piperazinones 14a−c, and 1,2,5,6-Tetrahydro-2-pyrazinones 15a−d

1	R^1	R^2	**2**	R^3	R^4	R^5	**3**	yield[a] (%)	**9**	yield[a] (%)	**14**	yield[a] (%)	**15**	yield[a,b] (%)	*T* (°C)
1c	CO_2Me	NH_2	**2a**	Ph	Ph						**14a**	65			90
1f	$POPh_2$	OEt	**2a**	Ph	Ph				**9d**	72					120
1g	$PO(OEt)_2$	OEt	**2a**	Ph	Ph				**9e**	66					120
1c	CO_2Me	NH_2	**2b**	*trans*-$(CH_2)_4$−									**15a**	42[a]	45
1d	CO_2Me	O*t*-Bu	**2b**	*trans*-$(CH_2)_4$−									**15b**	47[a]	45
1f	$POPh_2$	OEt	**2b**	*trans*-$(CH_2)_4$−					**9i**	93					120
1c	CO_2Me	NH_2	**2d**	H	H						**14b**	70	**15c**	62[b]	25
1d	CO_2Me	O-*t*-Bu	**2d**	H	H						**14c**	88	**15d**	60[b]	25
1a	CO_2Et	O-*t*-Bu	**2e**	H	H	Me	**3a**	80							
1d	CO_2Me	O-*t*-Bu	**2e**	H	H	Me	**3b**	76							
1a	CO_2Et	O-*t*-Bu	**2f**	H	H	Pr	**3c**	74							
1d	CO_2Me	O-*t*-Bu	**2f**	H	H	Pr	**3d**	70							

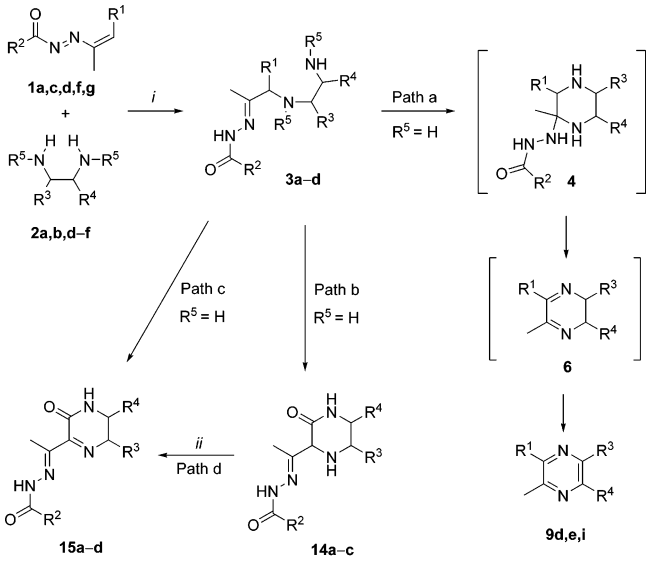
[a] Yields of pure products are based on 1,2-diaza-1,3-butadienes **1a**,**c**,**d**,**f**,**g**. [b] Yields of pure products are based on reagents **14b**,**c**.

2). 5,6-Dicyano-3-methyl-2-pyrazinecarboxylates **9m**,**n** were obtained by treatment of pure compounds **11a**,**b** or the crude reaction mixture with trifluoroacetic acid in acetonitrile under reflux (Scheme 5 and Table 2). The cyclization process takes place by further internal nucleophilic attack of the second amino group at the hydrazone carbon giving the intermediate **12**. Spontaneous elimination of the hydrazine residue leads to substituted 5,6-dicyano-3-methyl-1,4-dihydropyrazines **13** and then to pyrazines **9m**,**n** by oxidation with trifluoroacetic acid in acetonitrile under reflux.

We have also studied the reactions of 1,2-diaza-1,3-butadienes **1c**,**d**,**f**,**g** with diamine compounds **2a**,**b**,**d** under solvent-free conditions, in an attempt to obtain faster reaction times together with simple and environmentally friendly procedures.[27,28] To obtain homogeneous reaction media, the reactions were carried out at the melting point of diamines (Table 3). Surprisingly, the reactions showed a different unexpected behavior. In fact, 1,2-diaza-1,3-butadienes **1c**,**d** readily reacted with 6 equiv of diamines **2a**,**d** used as solvent and reagent to give substituted piperazinones **14a**−**c** (Scheme 6, path b, Table 3), while 1,2,5,6-tetrahydro-2-pyrazinones **15a**,**b** were directly collected in the case of the reaction between 1,2-diaza-1,3-butadienes **1c**,**d** and (±)-*trans*-1,2-diaminocyclohexane **2b** (Scheme 6, path c, Table 3).

The first step of this reaction is the nucleophilic attack of an amino group of 1,2-diamines **2a**,**d** at the terminal carbon atom of the heterodiene system of 1,2-diaza-1,3-butadienes **1c**,**d** with the formation of hydrazone 1,4-adducts (Michael type) **3**. The subsequent nucleophilic attack of the second amino group at the ester function with loss of an alcohol molecule produces piperazinones **14a**−**c** by ring closure (Scheme 6, path b, Table 3). In the case of the reaction between 1,2-diaza-1,3-butadienes **1c**,**d** and (±)-*trans*-1,2-diaminocyclohexane **2b**, spontaneous oxidation took place with the formation of 1,2,5,6-tetrahydro-2-pyrazinones **15a**,**b** without formation of the relevant products **14** (Scheme 6, path c). Oxidized compounds **15c**,**d** were obtained from **14b**,**c** by treatment with *N*-bromosuccinimide

SCHEME 6 [a]



R^1 = CO_2Me, CO_2Et, $POPh_2$, $PO(OEt)_2$;
R^2 = NH_2, OEt, O*t*-Bu; R^3 = R^4 = Ph, H, *trans*-$(CH_2)_4$−; R^5 = H, Me, Pr

[a] Reagents and conditions: (i) for **1a**,**d** + **2e**,**f**, solvent-free, for **1f**,**g** + **2a**, **1f** + **2b** (R^1 = $POPh_2$, $PO(OEt)_2$), solvent-free (path a), for **1c**,**d** + **2d** and **1c** + **2a** (R^1 = CO_2Me) (path b), for **1c**,**d** + **2b** (R^1 = CO_2Me) (path c); (ii) = for **14b**,**c**, NBS, MeOH, rt (path d).

(NBS) in methanol at room temperature[29,30] (Scheme 6, path d). It is noteworthy that pyrazinephosphine oxides **9d**,**i** and pyrazinephosphonate **9e** were directly prepared in good yields by reaction of 1,2-diaza-1,3-butadienes **1f**,**g** with 1,2-diamines **2a**,**b** in solvent-free conditions (Scheme 6, path a, Table 3). In these last cases, the absence of ester moiety at the terminal carbon of the heterodiene system induces the ring closure by attack of the second amino group at the hydrazone carbon of

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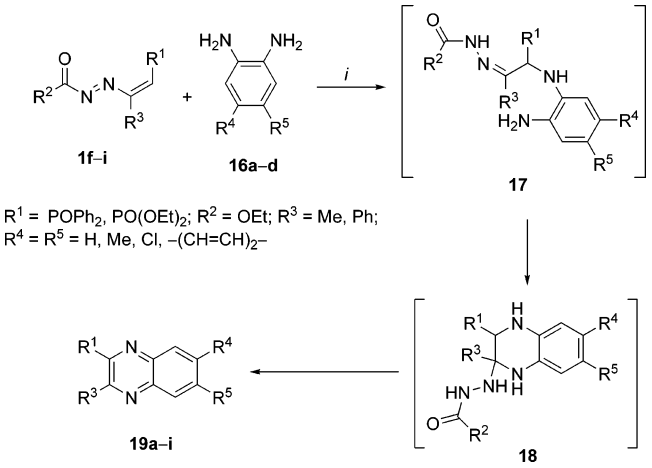
SCHEME 7 [a]



[a] Reagents and conditions: (i) = CH_2Cl_2, rt.

TABLE 4. Yields of Phosphorylated Quinoxalines 19a−i

1	R^1	R^2	R^3	16	R^4	R^5	19	yield[a] (%)
1f	$POPh_2$	OEt	Me	**16a**	H	H	**19a**	81
1g	$PO(OEt)_2$	OEt	Me	**16a**	H	H	**19b**	83
1h	$POPh_2$	OEt	Ph	**16a**	H	H	**19c**	91
1i	$PO(OEt)_2$	OEt	Ph	**16a**	H	H	**19d**	>98
1f	$POPh_2$	OEt	Me	**16b**	Me	Me	**19e**	90
1f	$POPh_2$	OEt	Me	**16c**	Cl	Cl	**19f**	93
1h	$POPh_2$	OEt	Ph	**16c**	Cl	Cl	**19g**	89
1f	$POPh_2$	OEt	Me	**16d**	$-(CH=CH)_2-$		**19h**	86
1g	$PO(OEt)_2$	OEt	Me	**16d**	$-(CH=CH)_2-$		**19i**	77

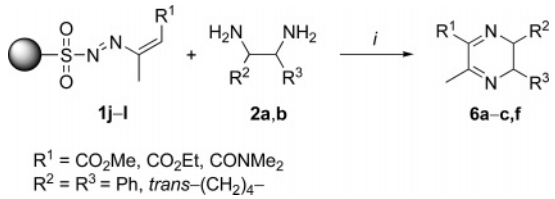
[a] Yield of isolated purified compounds **19** based on 1,2-diaza-1,3-butadienes **1f−i**.

the intermediate **3**. When the reaction between *N*,*N*′-dimethylethylenediamine **2e** and *N*,*N*′-di-*n*-propylethylenediamine **2f** with 1,2-diaza-1,3-butadienes **1a**,**d** was carried out under solvent-free conditions, only the hydrazone derivatives **3a−d** were formed in good yields (Scheme 6, Table 3). These latter compounds directly crystallized in the reaction medium probably avoiding the subsequent ring closure.

1,2-Diaza-1,3-butadienes containing a carboxylate group at the terminal carbon have been used as starting materials for the preparation of quinoxaline-2-carboxylates (Scheme 1, vide supra).[19] As a continuation of our work on the 1,4-addition reaction (Michael type) of 1,2-diaza-1,3-butadienes and on the chemistry of new phosphorus- and nitrogen-substituted heterocycles, we explored also the behavior of 1,2-diaza-1,3-butadienes derived from phosphine oxides and phosphonates, toward aromatic 1,2-diamines, for the preparation of quinoxalines containing a phosphine oxide or phosphonate moiety at the 2-position of the heterocyclic system (Scheme 1, vide supra). 1,2-Diaza-1,3-butadienes[13] **1f−i** easily reacted in methylene chloride at room temperature with 1,2-phenylendiamines **16a−d** to give quinoxaline-2-phosphine oxides and 2-phosphonates **19** in good to excellent yield (Scheme 7, Table 4). Addition of 1,2-phenylenediamine **16a** to the heterodiene system of **1f** led to the formation of quinoxaline-2-phosphine oxide **19a** in 81% yield (Scheme 7, Table 4).

The first step of the reaction is the nucleophilic attack of an amino group of 1,2-phenylendiamines **16a−d** on the terminal carbon of the heterodiene system of 1,2-diaza-1,3-butadienes **1f−i** with the formation of hydrazone 1,4-adduct intermediate (Michael type) **17** (Scheme 7). The subsequent nucleophilic

SCHEME 8 [a]



[a] Reagents and conditions: (i) = MeCN, rt.

TABLE 5. Yields of 5,6-Dihydropyrazines 6a−c,f Obtained in the Solid Phase

1	R^1	2	R^2	R^3	6	yield[a] (%)
1j	CO_2Et	**2a**	Ph	Ph	**6a**	18
1k	CO_2Me	**2a**	Ph	Ph	**6b**	21
1l	$CONMe_2$	**2a**	Ph	Ph	**6c**	20
1l	$CONMe_2$	**2b**	*trans*-$(CH_2)_4-$		**6f**	21

[a] Overall yields for the multistep process of pure isolated **6a−c**,**f** with respect to the starting polymer-bound *p*-toluenesulfonyl hydrazide.

attack of the second amino group at hydrazone carbon with loss of a hydrazine carboxylate residue affords 2-phosphorylated quinoxalines **19a−i** (Scheme 7). This strategy affords a very efficient entry to quinoxalinephosphine oxides **19a**,**c**,**e−h** and phosphonates **19b**,**d**,**i**. Quinoxalines directly substituted with phosphorus containing functional groups have received scarce attention.[31] To the best of our knowledge, the first synthesis of quinoxalines with a phosphonate group at the 2-position of the heterocyclic system is here described.

Based on the mild and simple conditions required from these reactions in the liquid phase, we have investigated these methodologies in solid-phase. Polymer-bound 1,2-diaza-1,3-butadienes **1j−l** prepared from polymer-bound *p*-toluenesulfonyl hydrazide[19a] readily reacted with 3 equiv of diamines **2a**,**b** in acetonitrile at room temperature to afford directly substituted 5,6-dihydropyrazines **6a−c**,**f** (Scheme 8, Table 5). The overall yields for the multistep process of these solid-phase reactions are comparable with the corresponding reactions in solution.

Conclusion

In summary, the procedures described here represent a convenient entry to functionalized tetrahydropyrazines, dihydropyrazines, pyrazines, piperazinones, quinoxaline-2-phosphine oxides, and phosphonates by 1,4-addition (Michael type) of 1,2-diamines to 1,2-diaza-1,3-butadienes in good yields. Although a number of methods are available for the synthesis of pyrazines and quinoxalines, a review of the literature revealed that the parent molecules are easily prepared but the corresponding substituted compounds are frequently difficult to obtain. The presence of different functional groups in many positions of these heterocycles is noteworthy making such compounds useful for further interesting structural modifications and suitable as intermediates for more complex structures or biologically active compounds.[1−8] Besides the mild and simple conditions of this procedure permit the access to valuable combinatorial libraries.

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In fact, many cyclic compounds previously obtained in solution from these reagents may now be reached by solid-phase reactions.

Experimental Section

General Methods. Reagent and solvent purification, workup procedures, and analyses were performed in general as described in the Supporting Information.

General Procedure for the Synthesis of Ethyl (5*R*,6*R*)-3-Methyl-5,6-diphenyl-1,4,5,6-tetrahydro-2-pyrazinecarboxylate 5a, Substituted 5,6-Dihydropyrazines 6a−f, and Substituted Pyrazines 9a−c,f−h (See Scheme 2, Path a). A stoichiometric amount of 1,2-diaza-1,3-butadiene **1a**−**e** (1 mmol) as a mixture of *E*/*Z* isomers[32] was slowly added to a solution of (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine **2a** (1 mmol) in MeCN (50 mL). Under the same conditions, compounds **1b**−**e** reacted with (±)-*trans*-1,2-diaminocyclohexane **2b**. The reaction was allowed to stand at room temperature (rt) with magnetic stirring until complete disappearance of 1,2-diaza-1,3-butadiene (monitored by silica gel TLC, 1 h). The solvent was then removed under reduced pressure, and the products **6a**−**f** were purified by chromatography on silica (elution mixture: cyclohexanes/ethyl acetate, 30:70). To obtain the oxidized products **9a**,**b**,**f**−**h**, the crude mixture or pure products **6a**,**b**,**d**−**f** (1 mmol) were dissolved with CH_2Cl_2 (150 mL), and PTAB (2 mmol) was slowly added. The reaction mixture was washed with H_2O (2 × 30 mL), the organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The products **9a**,**b** and **9f**−**h** were purified by chromatography on silica (elution mixture: cyclohexane/ethyl acetate, 60:40), and **9a**,**b** were crystallized from ethyl acetate−light petroleum ether (at 40−60 °C). To obtain product **9c**, the solution of 1,2-diaza-1,3-butadiene **1e** (1 mmol) and 1,2-diamine **2a** (1 mmol) was stirred until complete disappearance of the reagents (monitored by TLC). Trifluoroacetic acid was then added to the mixture until pH 1, and the solution was refluxed for 34 h. The solvent was removed under reduce pressure, and the crude was dissolved in ethyl acetate and washed with a saturated solution of Na_2CO_3 (2 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4. The product **9c** was purified by chromatography on silica (elution mixture: cyclohexane/ethyl acetate, 60:40) and crystallized from ethyl acetate−light petroleum ether (at 40−60 °C). In the case of the reaction between **1b** and **2a**, along with **6a**, product **5a** was isolated as a yellow oil by flash chromatography on silica gel and was immediately subjected to ^{1}H NMR analysis because of its poor stability.

Ethyl (5*R*,6*R*)-3-methyl-5,6-diphenyl-1,4,5,6-tetrahydro-2-pyrazinecarboxylate (5a): yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, ^3J = 7.2 Hz, 3H), 1.76 (s, 3H), 4.19 (q, ^3J = 7.2 Hz, 2H), 5.22 (t, ^3J = 8.4 Hz, 1H), 5.32 (t, ^3J = 8.4 Hz, 1H), 7.12−7.26 (m, 10H), 8.61 (d, ^3J = 8.4 Hz, 1H), 9.47 (d, ^3J = 8.4 Hz, 1H).

Ethyl (5*R*,6*R*)-3-methyl-5,6-diphenyl-5,6-dihydro-2-pyrazinecarboxylate (6a): yellow oil; IR (Nujol) ν_{max} 1742, 1677, 1564 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, ^3J = 7.2 Hz, 3H), 2.39 (d, ^5J = 2.4 Hz, 3H), 4.28 (dq, ^3J = 14.8 Hz, ^5J = 2.4 Hz, 1H), 4.36 (d, ^3J = 14.8 Hz, 1H), 4.43 (q, ^3J = 14.8 Hz, 2H), 6.93−6.98 (m, 4H), 7.17−7.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.8 (q), 62.4 (t), 65.4 (d), 66.0 (d), 127.3 (d), 127.4 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.3 (d), 139.4 (s), 140.2 (s), 153.7 (s), 155.5 (s), 164.2 (s); MS (EI) *m*/*z* 320 (67) [M$^+$], 291 (74), 275 (62), 247 (100). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.16; H, 6.21; N, 8.63.

Ethyl 3-methyl-5,6-diphenyl-2-pyrazinecarboxylate (9a): yellow powder; mp 67−71 °C; IR (Nujol) ν_{max} 1727, 1578, 1473, 1404, 1384, 1304 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, ^3J = 7.2 Hz, 3H), 2.91 (s, 3H), 4.50 (q, ^3J = 7.2 Hz, 2H), 7.28−7.32 (m, 6H), 7.48−7.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (q), 61.8 (t), 128.1 (d), 128.2 (d), 128.6 (d), 129.0 (d), 129.5 (d), 129.6 (d), 137.6 (s), 137.8 (s), 140.1 (s), 149.1 (s), 151.3 (s), 153.0 (s), 165.0 (s); MS (EI) *m*/*z* 318 (52) [M$^+$], 289 (8), 273 (4), 246 (100). Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.66; H, 5.59; N, 8.69.

General Procedure for the Synthesis of Phosphorylated Dihydropyrazines 6g−j, 7a,b, and 8b and Phosphorylated Pyrazines 9d,e,i,j (See Scheme 2, Path b and Scheme 3). To a stirred solution of 1,2-diaza-1,3-butadiene **1f**,**g** (1 mmol) as a mixture of *E*/*Z* isomers in CH_2Cl_2 (10 mL) was added dropwise a solution of (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine **2a**, (±)-*trans*-1,2-diaminocyclohexane **2b**, and (±)-*cis*-1,2-diaminocyclohexane **2c** (1 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature and followed by TLC (1−2 h). The solvent was evaporated under vacuum, and the crude products **6g**−**j** were purified by flash chromatography (silica gel, ethyl acetate/methanol 90:10), and crude products **7a**,**b** and **8b** were purified by flash chromatography (silica gel, ethyl acetate). Products **7b** and **8b** were obtained as a mixture of isomeric dihydropyridines in 70% yield. An example of pure **8b** was obtained after chromatography. In the case of reaction between **1f** and **2c**, only the pyrazine **9i** was isolated. In the case of the reaction between **1g** and **2c**, a mixture of dihydropyrazine **6j** and pyrazine **9j** was obtained after purification of the crude compound **6j** in a ratio of 3.7/1. Products **6j** and **9j** were immediately subjected to ^{1}H and ^{31}P analysis because of their instability. Pyrazine **9i** was obtained by oxidation of dihydropyrazine **6g** or **6i** (0.5 mmol) with *p*-benzoquinone (0.5 mmol, 54 mg) in dioxane (5 mL). The mixture was stirred and refluxed for 16 h. In the same way, oxidation of dihydropyrazines **7a** (0.5 mmol) and the mixture of dihydropyrazines **7b**, **8b** (0.5 mmol) with *p*-benzoquinone (0.5 mmol, 54 mg) in refluxing dioxane (5 mL) gave pyrazines **9d** and **9e**, respectively. The product **9d** was purified by flash chromatography (silica gel, ethyl acetate/hexanes 30:70), and products **9e**,**i** were purified by flash-chromatography (silica gel, ethyl acetate).

5-(Diphenylphosphinoyl)-6-methyl-2,3-diphenyl-1,2-dihydropyrazine (7a): yellow oil; IR (NaCl) ν_{max} 3196, 3052, 2919, 1722, 1658, 1514, 1493, 1434, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 5.66 (d, $^5J_{PH}$ = 4.2 Hz, 1H), 7.14−7.93 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 51.4, 110.3 (d, $^1J_{PC}$ = 166.6 Hz), 126.1, 126.9, 127.7, 127.8, 127.8, 127.8, 127.9, 128.2, 128.4, 128.5, 130.7, 130.7, 130.8, 130.8, 131.6, 131.7, 131.8, 131.9, 134.1, 134.7, 135.2, 135.7, 137.1, 139.9, 141.3 (d, $^3J_{PC}$ = 17.8 Hz), 145.4 (d, $^2J_{PC}$ = 27.4 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.7; MS (CI) *m*/*z* 449 (M$^+$ + 1, 100). Anal. Calcd for $C_{29}H_{25}N_2OP$: C, 77.66; H, 5.62; N, 6.25. Found: C, 77.72; H, 5.59; N, 6.28.

Diethyl (3-methyl-5,6-diphenyl-4,5-dihydropyrazin-2-yl)phosphonate (7b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03−1.40 (m, 6H), 2.34 (s, 3H), 3.88−4.29 (m, 4H), 5.67 (d, $^5J_{PH}$ = 4.0 Hz, 1H), 7.27−7.82 (m, 10H); ^{31}P NMR (160 MHz, $CDCl_3$) δ 18.3.

Diethyl (3-methyl-5,6-diphenyl-1,2-dihydropyrazin-2-yl)phosphonate (8b): colorless oil; IR (NaCl) ν_{max} 3228, 2983, 1744, 1450, 1402, 1247, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.41 (m, 6H), 2.32 (d, $^4J_{PH}$ = 2.4 Hz, 3H), 4.09−4.87 (m, 4H), 4.90 (d, $^2J_{PH}$ = 23.7 Hz, 1H), 7.27−7.79 (m, 10H), 10.08 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 14.1, 14.4, 16.2, 16.2, 16.3, 16.4, 16.4, 21.0, 59.3 (d, $^1J_{PC}$ = 146.8 Hz), 62.2, 62.3, 62.4, 63.1, 63.4, 63.5, 127.3, 127.6, 128.1, 128.2, 128.4, 128.7, 129.2, 130.4, 134.8 (d, $^4J_{PC}$ = 2.7 Hz), 150.8, 153.1, 154.3 (d, $^2J_{PC}$ = 9.1 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 14.8; MS (EI) *m*/*z* 384 (M$^+$, 5). Anal. Calcd for $C_{21}H_{25}N_2O_3P$: C, 65.61; H, 5.56; N, 7.29. Found: C, 65.71; H, 5.51; N, 7.27.

2-(Diphenylphosphinoyl)-3-methyl-5,6-diphenylpyrazine (9d): yellow oil; IR (NaCl) ν_{max} 1653, 1434, 1391, 1183 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (s, 3H), 7.13−7.89 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 127.2, 127.3, 127.3, 127.5, 127.7, 127.9, 128.1, 128.2, 128.3, 128.4, 128.6, 128.8, 128.9, 129.1, 129.2, 129.3,

(32) (a) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 671. (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 873.

129.4, 129.5, 129.6, 130.9, 131.0, 131.2, 131.3, 131.6, 131.8, 131.8, 132.0, 132.1, 132.3, 132.7, 137.4, 137.8, 145.4 (d, $^1J_{PC}$ = 129.0 Hz), 148.0 (d, $^3J_{PC}$ = 15.4 Hz), 151.8 (d, $^4J_{PC}$ = 2.89 Hz), 155.2 (d, $^2J_{PC}$ = 21.4 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 25.8; MS (EI) *m*/*z* 446 (M^+, 100). Anal. Calcd for $C_{29}H_{23}N_2OP$: C, 78.01; H, 5.19; N, 6.27. Found: C, 78.00; H, 5.22; N, 6.26.

General Procedure for the Synthesis of 1,4,5,6-Tetrahydropyrazine-3-methyl-2-carboxylates 5b−e and Ethyl 3-Methylpyrazine-2-carboxylate 9k (See Scheme 4). A stoichiometric amount of 1,2-diaza-1,3-butadiene **1a**,**d** (1 mmol) as a mixture of *E*/*Z* isomers was slowly added to a solution of *N*,*N*′-dimethylethylenediamine **2e** or *N*,*N*′-di-*n*-propylethylenediamine **2f** (1 mmol) in MeCN (50 mL). The reaction was allowed to stand at room temperature (rt) with magnetic stirring for 14 h. The solvent was then removed under reduced pressure and the products **5b−e** were purified by chromatography on silica, (elution mixture: cyclohexanes/ethyl acetate, 70:30).

To obtain ethyl 3-methylpyrazine-2-carboxylate **9k**, a solution of 1,2-diaza-1,3-butadienes **1a**,**b** (1 mmol) as a mixture of *E*/*Z* isomers in EtOH (10 mL) was added dropwise to a magnetically stirred solution of 1,2-diaminoethane **2d** (1 mmol) in EtOH (50 mL). The reaction was allowed to stand at rt until complete disappearance of 1,2-diaza-1,3-butadiene (monitored by silica gel TLC, 1 h). The reaction was then treated with Pd/C (110 mg, 5%) with magnetic stirring and refluxed for 14 h. The mixture was filtered and the solvent evaporated under reduced pressure. Product **9k** was purified by chromatography on silica gel (elution mixture: cyclohexane/ethyl acetate 70:30) and crystallized from ethyl acetate−light petroleum ether (at 40−60 °C).

Ethyl 1,3,4-trimethyl-1,4,5,6-tetrahydro-2-pyrazinecarboxylate (5b): yellow oil; IR (Nujol) ν_{max} 1688, 1574, 1456 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, ^3J = 7.2 Hz, 3H), 2.22 (s, 3H), 2.24 (s, 3H), 2.64−2.66 (m, 4H), 2.89 (s, 3H), 3.08−3.10 (m, 4H), 3.98 (q, ^3J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (q), 15.4 (q), 38.5 (q), 43.3 (q), 44.3 (t), 47.8 (t), 58.0 (t), 110.5 (s), 143.8 (s), 166.1 (s); MS (EI) *m*/*z* 198 (100) [M^+]. Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.72; H, 8.77; N, 15.23.

General Procedure for the Synthesis of 2-(Diphenylphosphinoyl)-3-methylpyrazine 9l (See Scheme 4). To a magnetically stirred solution of 1,2-diaza-1,3-butadiene **1f** (1 mmol) as a mixture of *E*/*Z* isomers in CH_2Cl_2 (10 mL) was added dropwise a solution of 1,2-diaminoethane **2d** (1.2 mmol) in CH_2Cl_2 (10 mL) at room temperature and under a nitrogen atmosphere. The reaction mixture was stirred at room temperature until complete disappearance of starting materials (1 h). The solvent was evaporated under vacuum. The crude product was unstable, and the dihydropyrazine was directly oxidized with 1,4-benzoquinone (1 mmol, 108 mg) in refluxing dioxane (10 mL). The reaction was washed with water (20 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic phase was evaporated under vacuum, and product **9l** was purified by flash chromatography (silica gel, ethyl acetate).

2-(Diphenylphosphinoyl)-3-methylpyrazine (9l): white solid; mp 136−137 °C; IR (KBr) ν_{max} 1434, 1183, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (s, 3H), 7.27−7.79 (m, 10H), 8.46−8.48 (m, 1H), 8.54 (dd, $^4J_{PH}$ = 3.9 Hz, $^3J_{HH}$ = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 128.6, 128.7, 129.2, 129.3, 131.0, 131.1, 132.2, 132.3, 132.5, 141.4 (d, $^3J_{PC}$ = 15.6 Hz), 145.1 (d, $^4J_{PC}$ = 3.5 Hz), 150.3 (d, $^1J_{PC}$ = 126.2 Hz), 159.6 (d, $^2J_{PC}$ = 20.6 Hz); ^{31}P NMR (120 MHz, $CDCl_3$) δ 27.2; MS (EI) *m*/*z* 294 (M^+, 70). Anal. Calcd for $C_{17}H_{15}N_2OP$: C, 69.38; H, 5.14; N, 9.52. Found: C, 69.46; H, 5.12; N, 9.55.

General Procedure for the Synthesis of α-[(2-Amino-1,2-dicyanovinyl)amino]hydrazones 11a,b and 5,6-Dicyanopyrazine-3-methyl-2-carboxylates 9m,n (See Scheme 5). A stoichiometric amount of 1,2-diaza-1,3-butadiene **1b**,**c** (1 mmol) as a mixture of *E*/*Z* isomers was slowly added to a solution of diaminomaleonitrile **10** (3 mmol) in MeCN (30 mL). The reaction was allowed to stand at room temperature (rt) with magnetic stirring for 96 h. The solvent was then removed under reduced pressure, and the products **11a**,**b** were purified by chromatography on silica, (elution mixture: cyclohexanes/ethyl acetate, 30:70). To obtain 5,6-dicyanopyrazine-3-methyl-2-carboxylates **9m**,**n**, the crude mixtures, or pure products **11a**,**b** (1 mmol), were dissolved with MeCN (30 mL), and trifluoroacetic acid was added until pH 1. The solution was refluxed for 30 h. The reaction mixture was neutralized with Na_2CO_3 and filtered, and the solvent was evaporated under reduced pressure. The products **9m**,**n** were purified by chromatography on silica (elution mixture: cyclohexane/ethyl acetate, 60:40).

Ethyl 5,6-dicyano-3-methyl-2-pyrazinecarboxylate (9m): white powder; mp 83−85 °C; IR (Nujol) ν_{max} 2242, 1743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, ^3J = 7.2 Hz, 3H), 2.93 (s, 3H), 4.50 (q, ^3J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (q), 23.2 (q), 63.5 (t), 112.3 (s), 112.4 (s), 129.9 (s), 133.4 (s), 145.9 (s), 158,5 (s), 162.4 (s); MS (EI) *m*/*z* 216 (35) [M^+], 188 (70), 170 (89), 144 (100). Anal. Calcd for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.50; H, 3.72; N, 25.88.

Ethyl 3-[2-(aminocarbonyl)hydrazono]-2-[(2-amino-1,2-dicyanovinyl)amino]butanoate (11a): white powder; mp 111−113 °C dec; IR (Nujol) ν_{max} 3486, 3374, 2220, 1746, 1688 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19 (t, ^3J = 7.2 Hz, 3H), 1.86 (s, 3H), 4.17 (q, ^3J = 7.2 Hz, 2H), 4.54 (d, ^3J = 9.6 Hz, 1H), 5.54 (d, ^3J = 9.6 Hz, 1H), 6.10 (s, 2H), 6.37 (br s, 2H), 9.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0 (q), 14.4 (q), 61.4 (t), 63.9 (d), 104.2 (s), 112.0 (s), 115.9 (s), 116.1 (s), 142.2 (s), 157.0 (s), 169.4 (s); MS (EI) *m*/*z* 293 (27) [M^+], 277 (29), 265 (32), 248 (25), 236 (100). Anal. Calcd for $C_{11}H_{15}N_7O_3$: C, 45.05; H, 5.15; N, 33.43. Found: C, 45.09; H, 5.14; N, 33.46.

General Procedure for the Synthesis of α-{Methyl[2-(methylamino)ethyl]amino}hydrazones 3a−d by Solvent-Free Reactions (See Scheme 6). 1,2-Diaza-1,3-butadiene **1a**,**d** (1 mmol) as a mixture of *E*/*Z* isomers was slowly added to 1,2-diamine **2e**,**f** (2 mmol). The reaction mixture was allowed to stand at room temperature (rt) with magnetic stirring until complete disappearance of 1,2-diaza-1,3-butadiene (monitored by silica gel TLC, 1 h). Pure hydrazones **3a−d** were crystallized from acetate−ethyl ether.

***tert*-Butyl 2-(3-ethoxy-1-methyl-2-methyl[2-(methylamino)-ethyl]amino-3-oxopropylidene)-1-hydrazinecarboxylate (3a):** white powder; mp 145−147 °C; IR (Nujol) ν_{max} 3238, 3165, 1748, 1707 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 (t, ^3J = 6.8 Hz, 3H), 1.41 (s, 9H), 1.82 (s, 3H), 2.20 (s, 3H), 2.48 (s, 3H), 3.30 (br s, 1H), 3.89 (s, 1H), 3.84−4.12 (m, 2H), 9.61 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9 (q), 14.1 (q), 28.0 (q), 38.9 (q), 51.5 (t), 59.8 (t), 73.4 (d), 79.2 (s), 149.6 (s), 152.8 (s), 169.7 (s); MS (EI) *m*/*z* 329 (4) [M^+ − 1], 300 (5), 286 (17), 243 (13), 230 (100). Anal. Calcd for $C_{15}H_{30}N_4O_4$: C, 54.53; H, 9.15; N, 16.91. Found: C, 54.48; H, 9.13; N, 16.89.

General Procedure for the Synthesis of Phosphorylated Pyrazines 9d,e,i and Piperazinones 14a−c and 15a−d by Solvent-Free Reactions (See Scheme 6, Paths a−d). Phosphorylated pyrazines **9d**,**e**,**i** were also obtained by solvent-free conditions when diamine **2a** or **2b** (1 mmol) was added dropwise to 1,2-diaza-1,3-butadiene **1f**,**g** (1 mmol). The reaction mixture was heated at 120 °C for 3 h, and the crude product **9d** was purified by flash chromatography (silica gel, ethyl acetate/hexanes 30:70); products **9e**,**i** were purified by flash chromatography (silica gel, ethyl acetate).

1,2-Diaza-1,3-butadienes **1c**,**d** (0.5 mmol) were slowly added to 1,2-diamines **2a**,**b**,**d** (3 mmol) heated in an oil bath (for temperatures, see Table 2) with magnetic stirring. After the complete disappearance of 1,2-diaza-1,3-butadiene (monitored by silica gel TLC, 20 min), the crude mixture was purified by chromatography on silica gel (elution mixture: ethyl acetate/methanol, 90:10) for the products **14a** and **15a**,**b**. For products **14b**,**c**, the excess 1,2-diamine **2d** was evaporated under reduced pressure and the crude reaction mixture was crystallized from ethyl acetate−methanol.

To a magnetically stirred solution of piperazinones **14b**,**c** (0.5 mmol) in methanol (20 mL) was slowly added a stoichiometric

amount of NBS (0.5 mmol). The conversion into pertinent 1,2,5,6-tetrahydro-2-pyrazinones **15a**,**b** occurred in 2 h. The solvent was evaporated under reduced pressure, and the crude reaction mixture was purified by chromatography on silica gel (elution mixture: ethyl acetate/methanol, 90:10) and was crystallized from ethyl acetate-methanol.

2-[1-(3-Oxo-2-piperazinyl)ethylidene]-1-hydrazinecarboxamide (14b): white powder; mp 149−152 °C; IR (Nujol) ν_{max} 3450, 3291, 3199, 1704, 1661, 1590 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74 (s, 3H), 2.69−2.76 (m, 2H), 2.88−2.93 (m, 1H), 3.01−3.07 (m, 1H), 3.16−3.23 (m, 1H), 3.82 (s, 1H), 6.28 (s, 2H), 7.77 (br s, 1H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0 (q), 41.1 (t), 42.0 (t), 65.6 (d), 146.8 (s), 157.2 (s), 168.1 (s); MS (EI) *m*/*z* 199 (3) [M$^+$], 182 (7), 169 (17), 149 (13), 139 (25), 123 (15), 111 (22), 97 (50), 83 (63), 69 (90), 57 (100). Anal. Calcd for $C_7H_{13}N_5O_2$: C, 42.20; H, 6.58; N, 35.16. Found: C, 42.39; H, 6.50; N, 35.31.

2-[1-(3-Oxo-3,4,5,6-tetrahydro-2-pyrazinyl)ethylidene]-1-hydrazinecarboxamide (15c): white powder; mp 188−190 °C; IR (Nujol) ν_{max} 3409, 3276, 3190, 1693, 1673, 1591, 1541 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (s, 3H), 3.21−3.25 (m, 2H), 3.67 (t, ^3J = 6.0 Hz, 2H), 6.21 (br s, 2H), 8.35 (br s, 1H), 9.66 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.4 (q), 37.9 (t), 48.1 (t), 142.2 (s), 155.9 (s), 156.7 (s), 161.0 (s); MS (EI) *m*/*z* 197 (6) [M$^+$], 181 (7), 169 (33), 151 (25), 125 (36), 111 (59), 97 (92), 83 (100). Anal. Calcd for $C_7H_{11}N_5O_2$: C, 42.64; H, 5.62; N, 35.51. Found: C, 42.81; H, 5.49; N, 35.59.

General Procedure for the Synthesis of 2-Phosphorylated Quinoxalines 19a−i (See Scheme 7). To a magnetic stirred solution of 1,2-diaza-1,3-butadienes **1f**−**i** (1 mmol) as a mixture of *E*/*Z* isomers in CH_2Cl_2 (10 mL) was added dropwise a solution of *o*-phenylendiamine **16a**, 4,5-dimethyl-*o*-phenylendiamine **16b**, 4,5-dichloro-*o*-phenylendiamine **16c**, 2,3-diaminonaphthalene **16d** (1.2 mmol) in CH_2Cl_2 (10 mL) at room temperature and under a nitrogen atmosphere. The reaction mixture was stirred at room temperature until complete disappearance of starting materials (1−3 h). The solvent was evaporated under vacuum and products **19a**,**f**,**h** were recrystallized from ethyl acetate, **19b**,**e**,**i** were purified by flash chromatography (silica gel, ethyl acetate), **19c**,**g** were purified by flash chromatography (silica gel, ethyl acetate/hexanes 50:50), and **19d** was purified by flash chromatography (silica gel, ethyl acetate/hexanes 90:10).

2-(Diphenylphosphinoyl)-3-methylquinoxaline (19a): brown solid; mp 159−160 °C; IR (KBr) ν_{max} 1540, 1434, 1188, 1122 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 7.27−8.05 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.3, 129.9, 130.6, 130.7, 131.1, 131.8, 132.0, 132.1, 132.2, 132.5, 139.8 (d, $^3J_{PC}$ = 17.6 Hz), 141.6 (d, $^4J_{PC}$ = 2.3 Hz), 151.1 (d, $^1J_{PC}$ = 124.0 Hz), 156.6 (d, $^2J_{PC}$ = 22.2 Hz); ^{31}P NMR (160 MHz, $CDCl_3$) δ 27.2; MS (EI) *m*/*z* 344 (M$^+$, 100). Anal. Calcd for $C_{21}H_{17}NOP$: C, 73.25; H, 4.96; N, 8.14. Found: C, 73.16; H, 4.92; N, 8.13.

General Procedure for the Synthesis of 3-Methyl-5,6-dihydropyrazine-2-carboxylate 6a−c,f in Solid Phase (See Scheme 8). To N=N-polymer-bound 1,2-diaza-1,3-butadienes[19a] **1j**−**l** in MeCN (20 mL) was added (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine **2a** or (±)-*trans*-1,2-diaminocyclohexane **2b** (3 equiv). The reaction mixture was allowed to stand at room temperature in MeCN under magnetic stirring for 4−6 h furnishing 3-methyl-5,6-dihydropyrazine-2-carboxylates **6** in solution. The resin was washed with MeCN (5 × 5 mL) and CH_2Cl_2 (5 × 5 mL). After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column (cyclohexane/ethyl acetate, 60:40) to give **6a**−**c**,**f** as yellow oils.

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Supporting Information Available: General experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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