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Solid-phase synthesis of 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones, 4-aminocarbonyl-pyrroles, 4-methoxy-1*H*-pyrazol-5(2*H*)-ones and 2-thiazolin-4-ones from polymer-bound 1,2-diaza-1,3-butadienes

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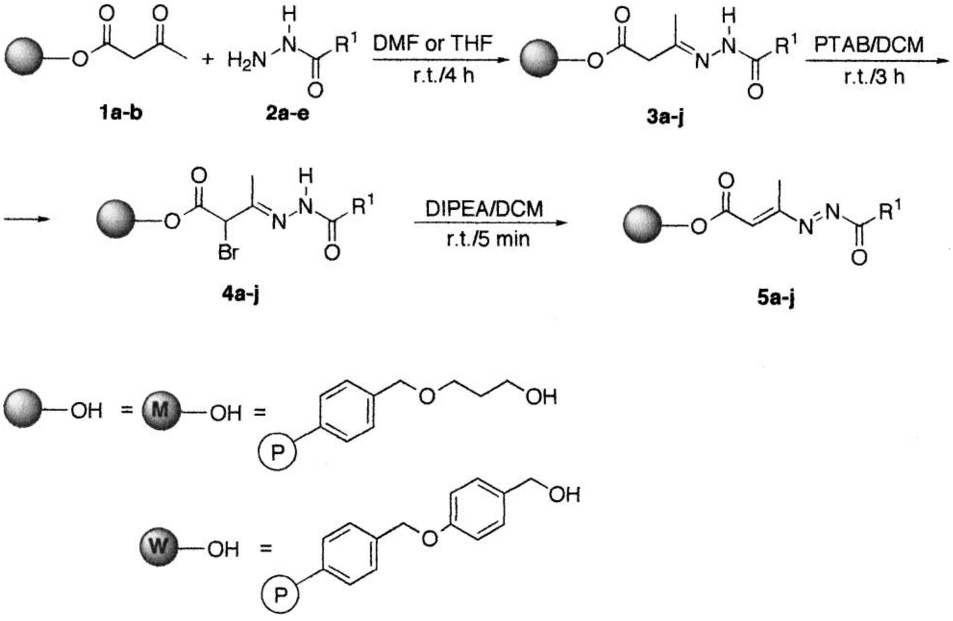
Abstract—The solid-phase synthesis of 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones, 4-aminocarbonyl-pyrroles, 4-methoxy-1*H*-pyrazol-5(2*H*)-ones and 2-thiazolin-4-ones using polymer-bound 1,2-diaza-1,3-butadienes is reported. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Combinatorial synthesis of small organic molecules has evolved rapidly in the last few years to become a new paradigm for contemporary drug discovery.[1] For this reason, increasing attention is currently devoted to this technique.[2] Some of us previously reported the use of modified Merrifield resin in the preparation of polymer-bound β-dicarbonyl derivatives from which some heterocyclic products were obtained.[3] Since 1,2-diaza-1,3-butadienes



Scheme 1.

Keywords: diaza compounds; Wang resin; pyrroles; pyrazol-5-ones; thiazolin-4-ones.

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Table 1. Polymer-bound 1,2-diaza-1,3-butadienes **5a–j**

1	●—OH	2	R^1	3,4,5	●—OH	R^1
a	M—OH	a	NH_2	a	M—OH	NH_2
b	W—OH	b	NHPh	b	M—OH	NHPh
		c	OMe	c	M—OH	O*t*-Bu
		d	OEt	d	M—OH	OEt
		e	O*t*-Bu	e	M—OH	OMe
				f	W—OH	NH_2
				g	W—OH	NHPh
				h	W—OH	O*t*-Bu
				i	W—OH	OEt
				j	W—OH	OMe

showed to be useful building blocks in organic chemistry,[4–7] we reported in a preliminary publication on the construction of modified Merrifield resin polymer-bound 1,2-diaza-1,3-butadiene derivatives from which some 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones were obtained.[8] Here in this report, we described an easy protocol for the synthesis of 4-aminocarbonylpyrroles, 4-methoxy-1*H*-pyrazol-5(2*H*)-ones, and 2-thiazolin-4-ones using modified Merrifield and Wang resin.

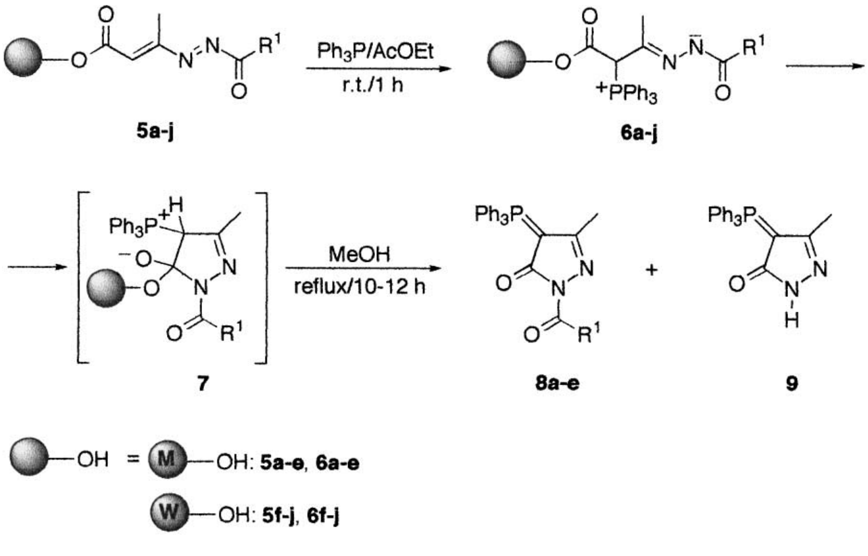
2. Results and discussion

Commercially available Merrifield resin was modified by introduction of a spacer with a free hydroxyl group to enhance reactivity of the substrates bound to the polymer.[3a] In connection with our ongoing investigations we found that commercial Wang resin can also be used with comparable efficiency and yields instead of the modified Merrifield one.

Both resins were treated with *tert*-butyl acetoacetate (toluene, reflux, 3 h) to give the polymer-bound β-ketoesters **1a–b**, in accordance with Witzeman's method.[9] Reaction of polymer-bound β-ketoesters **1a–b** with hydrazine derivatives **2a–e** (10 equiv., DMF or THF, room temperature, 4 h) led to corresponding hydrazones **3a–j** that were subjected to bromination with phenyltrimethylammonium tribromide[10] (PTAB) (1 equiv., dichloromethane (DCM), room temperature, 3 h) affording brominated hydrazones **4a–j**. Treatment of these compounds with *N*,*N*-diisopropylethylamine (DIPEA) (2 equiv., DCM, room temperature, 5 min) provided polymer-bound 1,2-diaza-1,3-butadienes **5a–j** (Scheme 1 and Table 1).

Addition of triphenylphosphine (10 equiv., AcOEt, room temperature, 1 h) to modified Merrifield resin polymer-bound 1,2-diaza-1,3-butadienes **5a–e** produced the corresponding 1,5-zwitterionic intermediates **6a–e**. In turn, they cyclize and then release 1-substituted **8a–e** and 1-unsubstituted 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **9** into solution by methanolysis (MeOH, reflux, 10–12 h) through the betaine form **7** (Scheme 2). The reactions with triphenylphosphine were carried out also using Wang resin polymer-bound 1,2-diaza-1,3-butadienes **5f–j** to achieve the same final products **8a–e** and **9** derived from 1,5-zwitterionic intermediates **6f–j** with comparable yields and reaction times. The overall yields of these solid-phase reactions are comparable with the corresponding reactions in solution (Table 2).[11]

Wang resin polymer-bound 1,2-diaza-1,3-butadienes **5f–h** and β-ketoamides **10a–d** (10 equiv., THF, room temperature, 4 h) in the presence of catalytic amounts of copper(II) dichloride gave polymer-bound 4-aminocarbonylpyrroles **13a–l**. In accordance with our previous findings, the nucleophilic attack of an activated methylene group on the 1,2-diazaheterodiene moiety in **5f–h** affords the 1,4-adduct **11** as an intermediate. This Michael-type addition is followed by an intramolecular addition of the nitrogen atom of the C═N group to the carbonyl group in δ position yielding the pyrroles **13a–l**. These reactions proceed smoothly under

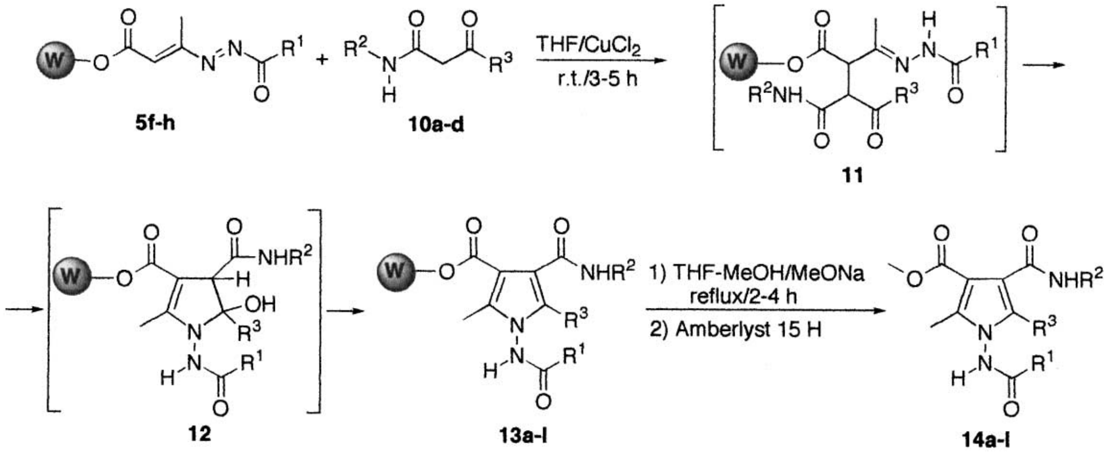


Scheme 2.

Table 2. Yields and reaction times of 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **8a–e** and **9a**

5,6	R^1	●—OH	**8**	R^1	Yields **8**+**9**[a,b,c] (%)	Yields **8**+**9**[a,b,d] (%)	Reaction time (h)[e]	Reflux time (h)[f]
a	NH_2	Ⓜ—OH	**a**	NH_2	42	41	1.0	11.0
b	NHPh	Ⓜ—OH	**b**	NHPh	36	34	1.0	10.0
c	O*t*-Bu	Ⓜ—OH	**c**	O*t*-Bu	18	21	1.0	12.0
d	OEt	Ⓜ—OH	**d**	OEt	12	13	1.0	12.0
e	OMe	Ⓜ—OH	**e**	OMe	17	18	1.0	11.0
f	NH_2	Ⓦ—OH						
g	NHPh	Ⓦ—OH						
h	O*t*-Bu	Ⓦ—OH						
i	OEt	Ⓦ—OH						
j	OMe	Ⓦ—OH						

[a] Overall yields for the multi-step process of isolated **8** and **9** in respect to the starting *tert*-butyl acetoacetate.
[b] Ratio **8**:**9** nearly 1:1.
[c] Yields obtained using modified Merrifield resin.
[d] Yields obtained using Wang resin.
[e] Reaction times are the same using modified Merrifield and Wang resins.
[f] Reflux times are the same using modified Merrifield and Wang resins.

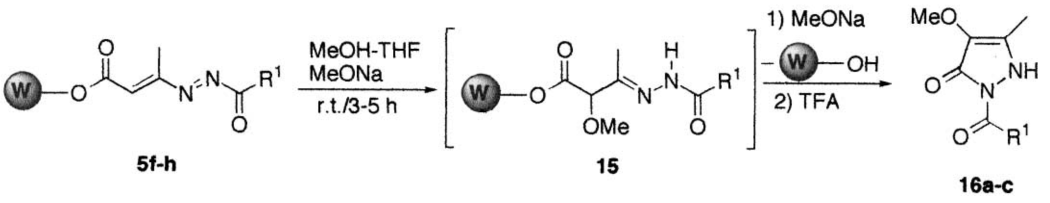


Scheme 3.

Table 3. Yields and reaction times of 4-aminocarbonyl-pyrroles **14a–l**

5	R^1	**10**	R^2	R^3	**13**, **14**	R^1	R^2	R^3	Yields **14**[a] (%)	Reaction time (h)	Reflux time (h)
f	NH_2	**a**	Ph	Me	**a**	NH_2	Ph	Me	64	4.5	2.0
g	NHPh	**b**	*p*-Cl–Ph	Me	**b**	NHPh	Ph	Me	45	4.0	4.0
h	O*t*-Bu	**c**	*p*-MeO–Ph	Me	**c**	O*t*-Bu	Ph	Me	22	3.0	3.0
		d	Ph	Ph	**d**	NH_2	*p*-Cl–Ph	Me	59	5.0	2.5
					e	NHPh	*p*-Cl–Ph	Me	35	4.5	3.0
					f	O*t*-Bu	*p*-Cl–Ph	Me	19	4.0	4.0
					g	NH_2	*p*-MeO–Ph	Me	44	5.0	3.0
					h	NHPh	*p*-MeO–Ph	Me	36	3.0	3.0
					i	O*t*-Bu	*p*-MeO–Ph	Me	19	3.5	2.0
					j	NH_2	Ph	Ph	72	4.5	4.0
					k	NHPh	Ph	Ph	37	4.0	3.5
					l	O*t*-Bu	Ph	Ph	17	5.0	3.5

[a] Overall yields for the multi-step process of isolated **14a–l** in respect to the starting *tert*-butyl acetoacetate.

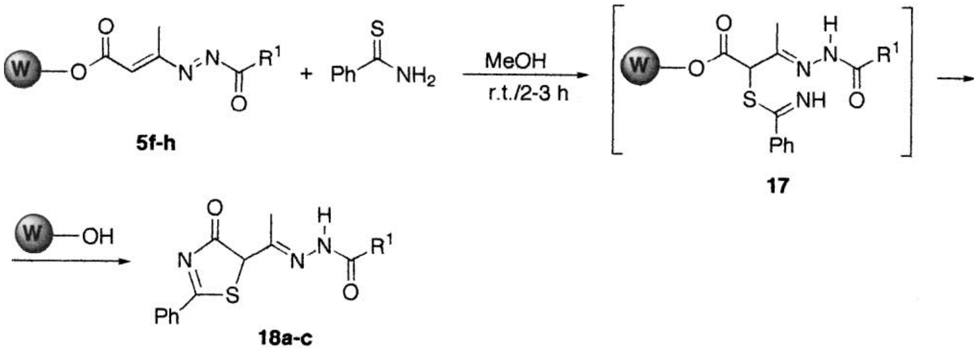


Scheme 4.

Table 4. Yields and reaction times of 4-methoxy-1*H*-pyrazol-5(2*H*)-ones **16a–c**

5	16	R^1	Yields[a] (%)	Reaction time (h)
f	**a**	NH_2	37	3.0
g	**b**	NHPh	42	3.5
h	**c**	O*t*-Bu	9	5.0

[a] Overall yields for the multi-step process of isolated **16a–c** in respect to the starting *tert*-butyl acetoacetate.



Scheme 5.

Table 5. Yields and reaction times of 2-thiazolin-4-ones **18a–c**

5	18	R^1	Yields[a] (%)	Reaction time (h)
f	**a**	NH_2	42	2.0
g	**b**	NHPh	40	3.0
h	**c**	O*t*-Bu	11	3.0

[a] Overall yields for the multi-step process of isolated **18a–c** in respect to the starting *tert*-butyl acetoacetate.

copper(II) ion catalysis. The polymer-bound 4-aminocarbonylpyrroles **13a–l** were cleaved from the resin by reflux (3 h) in MeOH–THF (1:4) in the presence of sodium methoxide (2 equiv.)[12] to give the 4-aminocarbonylpyrroles **14a–l** (Scheme 3). The overall yields of these solid-phase reactions are comparable with the corresponding reactions in solution (Table 3).[13–14]

Sodium methoxide (2 equiv., MeOH/THF 1:4, room temperature, 3 h) readily reacted with Wang resin polymer-bound 1,2-diaza-1,3-butadienes **5f–h**, affording α-methoxyhydrazones **15a–c** that, in the presence of a second equivalent of sodium methoxide produced 4-methoxy-1*H*-pyrazol-5(2*H*)-ones **16a–c**. The first step of the reaction consists of a 1,4-addition of the nucleophilic reagent to the azo–ene system. Then the intramolecular nucleophilic attack of the NH hydrazonic nitrogen atom at the alkoxycarbonyl group results in the pyrazole ring closure with loss of an alcohol molecule (Scheme 4). The overall yields of these solid-phase reactions are again comparable with the corresponding reactions in solution (Table 4).[15]

Addition of thiobenzamide (10 equiv., MeOH, room temperature, 3 h) to Wang resin polymer-bound 1,2-diaza-1,3-butadienes **5f–h** afforded 2-thiazolin-4-ones **18a–c**. The reaction clearly proceeds with the formation of 1,4-adduct intermediates via SH nucleophilic attack of the thioloimido function to the terminal carbon atom of the heterodiene system bearing a carboxylate group, on which a subsequent intramolecular NH nucleophilic attack with loss of an alcohol molecule leads to the thiazolinone ring closure (Scheme 5). The overall yields of these solid-phase reactions are comparable with the corresponding reactions in solution (Table 5).[16]

3. Conclusion

In conclusion, this paper describes a general protocol for the preparation of different polymer-bound 1,2-diaza-1,3-butadienes which are valuable substrates in synthetic organic chemistry. The mild and simple conditions of this procedure permit access to valuable combinatorial libraries. In fact, many cyclic compounds previously obtained in solution from these reagents may now be reached by solid-phase reactions. The synthesis of some 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones, 4-aminocarbonyl-pyrroles, 4-methoxy-1*H*-pyrazol-5(2*H*)-ones and 2-thiazolin-4-ones represents an example of such an application. With the exception of the cleavage steps, the reactions occur at room temperature, with formation of only minor by-products and simple manipulation of the reaction mixtures solely by filtration. The mild conditions of this reaction sequence makes it well amenable for automation.

4. Experimental

4.1. General

tert-Butyl acetoacetate, semicarbazide hydrochloride, sodium acetate, methyl carbazate, ethyl carbazate, *tert*-butyl carbazate, phenyltrimethylammonium tribromide, triphenylphosphine, acetoacetanilide, 4′-chloroaceto-acetanilide, *p*-acetoacetanisidide, 2-benzoylacetanilide, sodium methoxide and thiobenzamide were commercial materials and were used without further purification. Solvents were purchased and used without further purification with the exception of THF which was distilled from sodium hydroxide. Melting points were determined in open capillary tubes and are uncorrected. IR-FT spectra were obtained as Nujol mulls. Mass spectra were made at an ionizing voltage of 70 eV. All ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 and 100.56 MHz, respectively. Chemical shifts (δ_H) are reported relative to TMS as internal standard. All coupling constants (*J*) values are given in Hz. Chemical shifts (δ_C) are reported relative to DMSO-d_6 or $CDCl_3$ as internal standard in a broad band decoupled mode; the multiplicities were obtained by using 135 and 90° DEPT experiments to aid in assignment (q=methyl, t=methylene, d=methyne, s=quaternary). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; D_2O exch., exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35–70 μ for column chromatography.

4.2. General procedure for the synthesis of polymer-bound hydrazones 3a–j, α-bromohydrazones 4a–j, 1,2-diaza-1,3-butadienes 5a–j

Hydrazines **2a**–**e** (10 equiv.) were added to a magnetically stirred mixture of polymer-bound β-ketoester **1a** (0.300 g, 0.7 mmol per gram of resin) or **1b** (0.300 g, 1.2 mmol per gram of resin) in DMF (7 ml) in the case of hydrazines **2a**–**b** or THF in the case of hydrazines **2c**–**e**. The semicarbazide hydrochloride **2a** was treated with an equimolecular amount of sodium acetate to give the free form. The reaction was allowed to stand at room temperature for 4 h obtaining **3a**–**j**. The polymer-bound hydrazones **3a**–**j** were washed with MeOH, THF, DCM (3×5 ml). To polymer-bound hydrazones **3a**–**j** in DCM (150 ml) PTAB (1 equiv.) was added portionwise with magnetic stirring. The reaction was allowed to stand at room temperature for 3 h obtaining **4a**–**j**. The polymer-bound α-bromohydrazones **4a**–**j** were washed with MeOH and DCM (3×5 ml). To polymer-bound α-bromohydrazones **4a**–**j** in DCM (7 ml) was added under magnetic stirring DIPEA (2 equiv.). The reaction was allowed to stand at room temperature for 5 min obtaining **5a**–**j.** The polymer-bound 1,2-diaza-1,3-butadienes **5a**–**j** were washed with THF and DCM (3×5 ml)

4.3. General procedure for the synthesis of 1-substituted 8a–e and 1-unsubstituted 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones 9

To polymer-bound 1,2-diaza-1,3-butadienes **5a**–**j** in AcOEt (7 ml) (10 equiv.) triphenylphosphine was added under magnetic stirring. The reaction was allowed to stand at room temperature for 1 h obtaining the polymer-bound 1,5-zwitterionic intermediates **6a**–**j**, that were washed with DMF, AcOEt, MeOH (3×5 ml). Products **6a**–**j** in MeOH (10 ml) were refluxed under magnetic stirring for 10–12 h obtaining 1-substituted **8a**–**e** and 1-unsubstituted 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **9** by filtration in MeOH solution (>12–42%, using Merrifield resin; >13–41%, using Wang resin). After evaporation of the washing solvent under reduced pressure, the products were obtained by crystallization from ethyl acetate/petroleum ether (40–60°C). The final products **8a**–**e** and **9** were compared with authentic specimens by means of chromatographic and spectroscopic techniques (TLC, IR, NMR, MS).[11]

4.3.1. Compound 8a. White powder from ethyl acetate/petroleum ether (40–60°C); mp 336–337°C; IR: ν_{max} 3515, 3310, 1715, 1620 cm^{-1}; δ_H ($CDCl_3$) 1.41 (3H, s, CH_3), 5.18 (2H, br s, NH_2, D_2O exch.), 7.55–7.74 (15H, m, aromatic); δ_C ($CDCl_3$) 16.1 (q), 122.4 (s, $^1J_{CP}$=92.6 Hz), 129.8 (d, $^2J_{CP}$=10.6 Hz), 132.7 (s, $^1J_{CP}$=110.0 Hz), 134.0 (d), 134.2 (d, $^3J_{CP}$=10.8 Hz), 151.6 (s, $^2J_{CP}$=11.4 Hz), 152.7 (s), 169.0 (s, $^2J_{CP}$=18.2 Hz); MS: *m*/*z* (%) 401 (2) [M$^+$], 357 (100). Anal. Calcd for $C_{23}H_{20}N_3O_2P$: C, 68.82; H, 5.02; N, 10.47. Found: C, 68.91; H, 5.13; N, 10.36.

4.3.2. Compound 8b. White powder from ethyl acetate/petroleum ether (40–60°C); mp 273–275°C; IR: ν_{max} 3410, 1715, 1630 cm^{-1}; δ_H (DMSO-d_6) 1.24 (3H, s, CH_3), 7.02 (1H, t, *J*=7.6 Hz, aromatic), 7.28 (2H, t, *J*=7.6 Hz, aromatic), 7.48 (2H, d, *J*=7.6 Hz, aromatic), 7.66–7.82 (15H, m, aromatic), 11.54 (1H, s, NH, D_2O exch.); δ_C (DMSO-d_6) 16.0 (q), 118.0 (d), 119.9 (d), 122.4 (s, $^1J_{CP}$=92.6 Hz), 123.7 (d), 129.6 (s), 130.4 (d, $^2J_{CP}$=12.9 Hz), 133.7 (s, $^1J_{CP}$=102.0 Hz), 134.6 (d, $^3J_{CP}$=10.6 Hz), 135.1 (d), 138.9 (s), 151.6 (s, $^2J_{CP}$=12.1 Hz), 169.0 (s, $^2J_{CP}$=19.0 Hz); MS: *m*/*z* (%) 477 (2) [M$^+$], 357 (100). Anal. Calcd for $C_{29}H_{24}N_3O_2P$: C, 72.95; H, 5.07; N, 8.80. Found: C, 72.91; H, 5.15; N, 8.77.

4.3.3. Compound 8c. White powder from ethyl acetate/petroleum ether (40–60°C); mp 334–336°C; IR: ν_{max} 1745, 1615 cm^{-1}; δ_H (DMSO-d_6) 1.15 (3H, s, CH_3), 1.45 (9H, s, CO_2t-Bu), 7.62–7.75 (15H, m, aromatic); δ_C (DMSO-d_6) 14.8 (q), 28.6 (q), 81.3 (s), 123.1 (s, $^1J_{CP}$=92.0 Hz), 130.1 (d, $^2J_{CP}$=12.0 Hz), 133.5 (s, $^1J_{CP}$=102.0 Hz), 134.3 (d), 134.5 (d, $^3J_{CP}$=10.6 Hz), 151.4 (s, $^2J_{CP}$=12.2 Hz), 159.1 (s), 168.0 (s, $^2J_{CP}$=19.0 Hz); MS: *m*/*z* (%) 458 (1) [M$^+$], 357 (100). Anal. Calcd for $C_{27}H_{27}N_2O_3P$: C, 70.73; H, 5.94; N, 6.11. Found: C, 70.83; H, 5.87; N, 6.23.

4.3.4. Compound 8d. White powder from ethyl acetate/petroleum ether (40–60°C); mp 227–230°C; IR: ν_{max} 1745, 1625 cm^{-1}; δ_H (DMSO-d_6) 1.19 (3H, s, CH_3), 1.67

(3H, t, J=7.0 Hz, $CO_2CH_2\mathit{CH_3}$), 4.50 (2H, q, J=7.0 Hz, $CO_2\mathit{CH_2}CH_3$), 7.65–7.85 (15H, m, aromatic); δ_C (DMSO-d_6) 11.9 (q), 14.7 (q), 62.1 (t), 123.0 (s, $^1J_{CP}$=92.2 Hz), 129.9 (d, $^2J_{CP}$=11.8 Hz), 133.7 (s, $^1J_{CP}$=102.0 Hz), 134.3 (d), 135.0 (d, $^3J_{CP}$=10.4 Hz), 151.4 (s, $^2J_{CP}$=12.0 Hz), 159.5 (s), 168.2 (s, $^2J_{CP}$=19.0 Hz); MS: m/z (%) 430 (1) [M^+], 357 (100). Anal. Calcd for $C_{25}H_{23}N_2O_3P$: C, 69.76; H, 5.39; N, 6.51. Found: C, 69.70; H, 5.51; N, 6.58.

4.3.5. Compound 8e. White powder from ethyl acetate/petroleum ether (40–60°C); mp 231–233°C; IR: I_{max} 1750, 1630 cm^{-1}; δ_H (DMSO-d_6) 1.18 (3H, s, CH_3), 3.51 (3H, s, CO_2CH_3), 7.60–7.73 (15H, m, aromatic); δ_C (DMSO-d_6) 14.6 (q), 53.6 (q), 122.6 (s, $^1J_{CP}$=92.0 Hz), 129.4 (d, $^2J_{CP}$=12.0 Hz), 133.3 (s, $^1J_{CP}$=102.0 Hz), 134.4 (d), 134.8 (d, $^3J_{CP}$=10.6 Hz), 151.7 (s, $^2J_{CP}$=12.2 Hz), 159.8 (s), 168.0 (s, $^2J_{CP}$=19.0 Hz); MS: m/z (%) 416 (4) [M^+], 357 (100). Anal. Calcd for $C_{24}H_{21}N_2O_3P$: C, 69.22; H, 5.05; N, 6.73. Found: C, 69.31; H, 5.15; N, 6.81.

4.3.6. Compound 9. White powder from ethyl acetate/petroleum ether (40–60°C); mp 336–338°C; IR: ν_{max} 3210, 3130, 1600 cm^{-1}; δ_H (DMSO-d_6) 1.38 (3H, s, CH_3), 7.42–8.03 (16H, m, aromatic and NH, D_2O exch.); δ_C (DMSO-d_6) 15.9 (q), 123.0 (s, $^1J_{CP}$=92.6 Hz), 130.2 (d, $^2J_{CP}$=11.6 Hz), 132.8 (s, $^1J_{CP}$=108.0 Hz), 133.8 (d), 134.3 (d, $^3J_{CP}$=10.4 Hz), 151.4 (s, $^2J_{CP}$=12.0 Hz), 168.8 (s, $^2J_{CP}$=18.8 Hz); MS: m/z (%) 358 (89) [M^+], 357 (100). Anal. Calcd for $C_{22}H_{19}N_2OP$: C, 73.73; H, 5.34; N, 7.82. Found: C, 73.81; H, 5.51; N, 7.73.

4.4. General procedure for the synthesis of 4-aminocarbonyl-pyrroles 14a–l

In the presence of a catalytic amount of copper(II) chloride (0.5 equiv.) β-ketoamides **10a–d** (10 equiv.) were added to polymer-bound 1,2-diaza-1,3-butadienes **5f–h** in THF (7 ml) under magnetic stirring. The reaction was allowed to stand at room temperature for 3–5 h obtaining **13a–l** that were washed with MeOH, THF and DCM (3×5 ml). In the presence of sodium methoxide (2 equiv.) in MeOH–THF (2:8 ml)[12] the polymer-bound 4-amido-pyrroles **13a–l** were refluxed, under magnetic stirring, for 2–4 h obtaining by filtration 4-aminocarbonyl-pyrroles **14a–l** in solution (>17–72%). The residue resin was washed with MeOH and THF (3×5 ml). The solvent was removed in vacuo, and the residue, dissolved in MeOH, was treated, under magnetic stirring, with Amberlyst 15-H. The reaction was allowed to stand at room temperature for 1 h obtaining **14a–l**. After evaporation of the washing solvents under reduced pressure products **14a–l** were obtained by crystallization from ethyl acetate/petroleum ether (40–60°C). The final products **14a–l** were compared with authentic specimens by means of chromatographic and spectroscopic techniques (TLC, IR, NMR, MS).[13,14]

4.4.1. Compound 14a. White powder from ethyl acetate/petroleum ether (40–60°C); mp 242–245°C; IR: ν_{max} 3395, 3250, 3195, 1710, 1655 cm^{-1}; δ_H (DMSO-d_6) 2.14 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.67 (3H, s, CO_2CH_3), 6.28 (2H, br s, NH_2, D_2O exch.), 7.00 (1H, t, J=7.6 Hz, aromatic), 7.28 (2H, t, J=7.6 Hz, aromatic), 7.67 (2H, d, J=7.6 Hz, aromatic), 9.30 (1H, br s, NH, D_2O exch.), 10.26 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.4 (q), 11.2 (q), 51.6 (q), 107.6 (s), 116.8 (s), 120.2 (d), 123.6 (d), 129.0 (d), 132.5 (s), 136.4 (s), 140.2 (s), 157.4 (s), 163.7 (s), 165.7 (s); MS: m/z (%) 330 (24) [M^+], 313 (7), 238 (100). Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.16; H, 5.50; N, 16.97. Found: C, 58.32; H, 5.61; N, 16.88.

4.4.2. Compound 14b. White powder from ethyl acetate/petroleum ether (40–60°C); mp 228–230°C; IR: ν_{max} 3300, 3210, 1690, 1655, 1630 cm^{-1}; δ_H (DMSO-d_6) 2.16 (3H, s, CH_3), 2.34 (3H, s, CH_3), 3.65 (3H, s, CO_2CH_3), 6.97–7.02 (2H, m, aromatic), 7.25–7.29 (4H, m, aromatic), 7.45 (2H, d, J=7.6 Hz, aromatic), 7.67 (2H, d, J=7.6 Hz, aromatic), 9.34 (1H, br s, NH, D_2O exch.), 9.53 (1H, br s, NH, D_2O exch.), 10.21 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.5 (q), 11.4 (q), 51.5 (q), 107.8 (s), 116.2 (s), 119.5 (d), 119.8 (d), 122.9 (d), 123.4 (d), 129.2 (d), 129.5 (d), 130.4 (s), 133.5 (s), 136.5 (s), 139.6 (s), 154.5 (s), 164.4 (s), 165.1 (s); MS: m/z (%) 406 (12) [M^+], 314 (100). Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78. Found: C, 65.22; H, 5.40; N, 13.62.

4.4.3. Compound 14c. White powder from ethyl acetate/petroleum ether (40–60°C); mp 188–190°C; IR: ν_{max} 3300, 1735, 1700, 1665 cm^{-1}; δ_H (DMSO-d_6) 1.36 (9H, s, CO_2t-Bu), 2.14 (3H, s, CH_3), 2.30 (3H, s, CH_3), 3.65 (3H, s, CO_2CH_3), 7.02 (1H, t, J=7.6 Hz, aromatic), 7.26 (2H, t, J=7.6 Hz, aromatic), 7.66 (2H, d, J=7.6 Hz, aromatic), 10.13 (1H, s, NH, D_2O exch.), 10.52 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.2 (q), 11.0 (q), 28.3 (q), 51.7 (q), 81.7 (s), 108.0 (s), 116.6 (s), 120.1 (d), 123.6 (d), 129.2 (d), 131.7 (s), 136.0 (s), 140.4 (s), 156.3 (s), 164.1 (s), 165.4 (s); MS: m/z (%) 387 (61) [M^+], 295 (89), 269 (100). Anal. Calcd for $C_{20}H_{25}N_3O_5$: C, 61.99; H, 6.51; N, 10.85. Found: C, 61.78; H, 6.31; N, 10.91.

4.4.4. Compound 14d. White powder from ethyl acetate/petroleum ether (40–60°C); mp 298–299°C; IR: ν_{max} 3425, 3275, 3210, 1680, 1660, 1630 cm^{-1}; δ_H (DMSO-d_6) 2.13 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.63 (3H, s, CO_2CH_3), 6.29 (2H, br s, NH_2, D_2O exch.), 7.33 (2H, d, J=8.4 Hz, aromatic), 7.69 (2H, d, J=8.4 Hz, aromatic), 9.30 (1H, br s, NH, D_2O exch.), 10.29 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.5 (q), 11.3 (q), 51.7 (q), 107.4 (s), 115.7 (s), 121.4 (d), 127.0 (s), 129.1 (d), 132.9 (s), 137.1 (s), 139.4 (s), 157.5 (s), 164.4 (s), 165.6 (s); MS: m/z (%) 366 (12) [M^+ +2], 364 (32) [M^+], 238 (100). Anal. Calcd for $C_{16}H_{17}N_4O_4Cl$: C, 52.68; H, 4.70; N, 15.36. Found: C, 52.49; H, 4.81; N, 15.41.

4.4.5. Compound 14e. White powder from ethyl acetate/petroleum ether (40–60°C); mp 220–222°C; IR: ν_{max} 3300, 3250, 3205, 1690, 1650, 1625 cm^{-1}; δ_H (DMSO-d_6) 2.17 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.63 (3H, s, CO_2CH_3), 6.99 (1H, t, J=7.6 Hz, aromatic), 7.27 (2H, t, J=7.6 Hz, aromatic), 7.33 (2H, d, J=8.8 Hz, aromatic), 7.46 (2H, d, J=7.6 Hz, aromatic), 7.73 (2H, d, J=8.8 Hz, aromatic), 9.28 (1H, s, NH, D_2O exch.), 9.51 (1H, s, NH, D_2O exch.), 10.32 (1H, s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.5 (q), 11.3 (q), 51.6 (q), 107.8 (s), 116.0 (s), 119.6 (d), 121.3 (d), 123.2 (s), 126.9 (d), 129.1 (d), 129.4 (d), 132.6 (s), 137.0 (s), 139.5 (s), 139.8 (s), 154.4 (s), 164.5 (s), 165.0 (s); MS: m/z (%) 442 (3)

$[M^+ + 2]$, 440 (10) $[M^+]$, 328 (59), 314 (100). Anal. Calcd for $C_{22}H_{21}N_4O_4Cl$: C, 59.93; H, 4.80; N, 12.71. Found: C, 59.88; H, 4.88; N, 12.83.

4.4.6. Compound 14f. White powder from ethyl acetate/petroleum ether (40–60°C); mp 198–200°C; IR: ν_{max} 3310, 3180, 1755, 1690, 1665 cm^{-1}; δ_H (DMSO-d_6) 1.37 (9H, s, CO_2*t*-Bu), 2.11 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.62 (3H, s, CO_2CH_3), 7.34 (2H, d, J=8.8 Hz, aromatic), 7.69 (2H, d, J=8.8 Hz, aromatic), 10.25 (1H, s, NH, D_2O exch.), 10.72 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.2 (q), 11.0 (q), 28.3 (q), 51.7 (q), 81.3 (s), 108.0 (s), 116.3 (s), 121.4 (d), 127.1 (s), 129.1 (d), 131.6 (s), 136.1 (s), 139.4 (s), 156.4 (s), 164.2 (s), 165.1 (s); MS: *m/z* (%) 423 (3) $[M^+ + 2]$, 421 (11) $[M^+]$, 360 (4), 358 (13), 347 (4), 345 (13), 293 (100). Anal. Calcd for $C_{20}H_{24}N_3O_5Cl$: C, 56.99; H, 5.74; N, 9.98. Found: C, 56.77; H, 5.81; N, 10.01.

4.4.7. Compound 14g. White powder from ethyl acetate/petroleum ether (40–60°C); mp 253–255°C; IR: ν_{max} 3395, 3250, 3190, 1690, 1645 cm^{-1}; δ_H (DMSO-d_6) 2.14 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.65 (3H, s, CO_2CH_3), 3.71 (3H, s, OCH_3), 6.28 (2H, s, NH_2, D_2O exch.), 6.86 (2H, d, J=8.4 Hz, aromatic), 7.57 (2H, d, J=8.4 Hz, aromatic), 9.28 (1H, s, NH, D_2O exch.), 10.04 (1H, s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.5 (q), 11.3 (q), 51.6 (q), 55.8 (q), 107.4 (s), 114.4 (d), 116.1 (s), 121.5 (d), 132.4 (s), 133.7 (s), 136.9 (s), 155.6 (s), 157.6 (s), 163.8 (s), 165.7 (s); MS: *m/z* (%) 360 (30) $[M^+]$, 317 (5), 238 (100). Anal. Calcd for $C_{17}H_{20}N_4O_5$: C, 56.66; H, 5.59; N, 15.55. Found: C, 56.81; H, 5.41; N, 15.61.

4.4.8. Compound 14h. White powder from ethyl acetate/petroleum ether (40–60°C); mp 236–238°C; IR: ν_{max} 3305, 3220, 1730, 1675, 1625 cm^{-1}; δ_H (DMSO-d_6) 2.16 (3H, s, CH_3), 2.33 (3H, s, CH_3), 3.64 (3H, s, CO_2CH_3), 3.70 (3H, s, OCH_3), 6.85 (2H, d, J=8.4 Hz, aromatic), 6.98 (1H, t, J=7.6 Hz, aromatic), 7.27 (2H, t, J=7.6 Hz, aromatic), 7.45 (2H, d, J=7.6 Hz, aromatic), 7.60 (2H, d, J=8.4 Hz, aromatic), 9.30 (1H, s, NH, D_2O exch.), 9.50 (1H, s, NH, D_2O exch.), 10.06 (1H, s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.5 (q), 11.4 (q), 51.6 (q), 55.8 (q), 107.7 (s), 114.3 (d), 116.3 (s), 119.5 (d), 121.3 (d), 129.4 (d), 132.2 (s), 133.8 (s), 136.8 (s), 139.8 (s), 154.4 (s), 155.6 (s), 163.9 (s), 165.2 (s); MS: *m/z* (%) 436 (25) $[M^+]$, 404 (14), 328 (56), 314 (100). Anal. Calcd for $C_{23}H_{24}N_4O_5$: C, 63.29; H, 5.54; N, 12.84. Found: C, 63.38; H, 5.61; N, 12.71.

4.4.9. Compound 14i. White powder from ethyl acetate/petroleum ether (40–60°C); mp 208–210°C; IR: ν_{max} 3340, 3155, 1745, 1690, 1655 cm^{-1}; δ_H (DMSO-d_6) 1.37 (9H, s, CO_2*t*-Bu), 2.12 (3H, s, CH_3), 2.30 (3H, s, CH_3), 3.64 (3H, s, CO_2CH_3), 3.71 (3H, s, OCH_3), 6.86 (2H, d, J=8.4 Hz, aromatic), 7.57 (2H, d, J=8.4 Hz, aromatic), 10.00 (1H, s, NH, D_2O exch.), 10.71 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.2 (q), 11.0 (q), 28.4 (q), 51.7 (q), 55.8 (q), 81.8 (s), 107.9 (s), 114.4 (d), 116.7 (s), 121.5 (d), 131.3 (s), 133.6 (s), 135.9 (s), 155.7 (s), 156.4 (s), 163.6 (s), 165.3 (s); MS: *m/z* (%) 417 (21) $[M^+]$, 361 (11), 345 (5), 317 (16), 295 (18), 239 (100). Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.55; H, 6.41; N, 10.15.

4.4.10. Compound 14j. White powder from ethyl acetate/petroleum ether (40–60°C); mp 237–238°C; IR: ν_{max} 3435, 3275, 3220, 1730, 1680, 1640 cm^{-1}; δ_H (DMSO-d_6) 2.36 (3H, s, CH_3), 3.62 (3H, s, CO_2CH_3), 6.18 (2H, s, NH_2, D_2O exch.), 6.98 (1H, t, J=7.6 Hz, aromatic), 7.20–7.36 (5H, m, aromatic), 7.44 (2H, d, J=7.6 Hz, aromatic), 7.53 (2H, d, J=7.6 Hz, aromatic), 9.36 (1H, s, NH, D_2O exch.), 10.05 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 11.2 (q), 51.7 (q), 108.2 (s), 119.1 (s), 120.1 (d), 123.6 (s), 123.7 (d), 128.5 (d), 128.6 (d), 129.1 (d), 130.1 (d), 132.4 (s), 137.7 (s), 140.3 (s), 157.6 (s), 164.6 (s), 164.8 (s); MS: *m/z* (%) 392 (10) $[M^+]$, 300 (100). Anal. Calcd for $C_{21}H_{20}N_4O_4$: C, 64.28; H, 5.14; N, 14.28. Found: C, 64.35; H, 5.07; N, 14.31.

4.4.11. Compound 14k. White powder from ethyl acetate/petroleum ether (40–60°C); mp 244–246°C; IR: ν_{max} 3380, 3270, 3200, 1720, 1695, 1645 cm^{-1}; δ_H (DMSO-d_6) 2.43 (3H, s, CH_3), 3.64 (3H, s, CO_2CH_3), 6.96–7.58 (15H, m, aromatic), 9.17 (1H, br s, NH, D_2O exch.), 9.56 (1H, s, NH, D_2O exch.), 10.13 (1H, s, NH, D_2O exch.); δ_C (DMSO-d_6) 11.2 (q), 51.7 (q), 108.4 (s), 119.2 (s), 119.4 (d), 120.1 (d), 123.1 (d), 123.7 (s), 128.6 (d), 128.7 (d), 129.2 (d), 129.5 (d), 130.1 (d), 130.3 (d), 132.6 (s), 137.8 (s), 139.8 (s), 140.3 (s), 154.7 (s), 164.5 (s), 164.8 (s); MS: *m/z* (%) 468 (15) $[M^+]$, 376 (100). Anal. Calcd for $C_{27}H_{24}N_4O_4$: C, 69.20; H, 5.17; N, 11.96. Found: C, 69.21; H, 5.23; N, 11.78.

4.4.12. Compound 14l. White powder from ethyl acetate/petroleum ether (40–60°C); mp 180–183°C; IR: ν_{max} 3290, 1735, 1705, 1655 cm^{-1}; δ_H (DMSO-d_6) 1.36 (9H, s, CO_2*t*-Bu), 2.37 (3H, s, CH_3), 3.66 (3H, s, CO_2CH_3), 6.97 (1H, t, J=7.6 Hz, aromatic), 7.24 (2H, t, J=7.6 Hz, aromatic), 7.30–7.42 (5H, m, aromatic), 7.56 (2H, d, J=7.6 Hz, aromatic), 10.13 (1H, s, NH, D_2O exch.), 10.41 (1H, s, NH, D_2O exch.); δ_C (DMSO-d_6) 10.9 (q), 28.5 (q), 51.6 (q), 81.6 (s), 108.6 (s), 119.3 (s), 119.8 (d), 123.5 (s), 128.7 (d), 129.1 (d), 130.0 (d), 132.0 (s), 136.9 (s), 140.4 (s), 155.0 (s), 164.2 (s), 164.4 (s); MS: *m/z* (%) 449 (7) $[M^+]$, 357 (47), 349 (100). Anal. Calcd for $C_{25}H_{27}N_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.72; H, 6.12; N, 9.24.

4.5. General procedure for the synthesis of 4-methoxy-1*H*-pyrazol-5(2*H*)-ones 16a–c

To polymer-bound 1,2-diaza-1,3-butadienes **5g–h** in THF (7 ml) sodium methoxide (2 equiv.) was added under magnetic stirring. The reaction was allowed to stand at room temperature for 3–5 h obtaining **16a–c** in solution (>9–42%). The resin was washed with MeOH, THF and DCM (3×5 ml) and the reaction mixture was acidified by addition of trifluoroacetic acid (1 equiv.). After evaporation of the washing solvents under reduced pressure products **16a–c** were obtained by crystallization from ethyl acetate/petroleum ether (40–60°C). The final products **16a–c** were compared with authentic specimens by means of chromatographic and spectroscopic techniques (TLC, IR, NMR, MS).[15]

4.5.1. Compound 16a. White powder from ethyl acetate/petroleum ether (40–60°C); mp 131–132°C; IR: ν_{max} 3360, 3080, 1690, 1625, 1560 cm^{-1}; δ_H (DMSO-d_6) 2.08 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 7.78 and 8.22 (2H, 2 s, NH_2, D_2O exch.), 11.34 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 9.0

(q), 60.0 (q), 126.8 (s), 140.4 (s), 149.2 (s), 157.3 (s); MS: *m*/*z* (%) 177 (19) [M$^+$], 128 (100). Anal. Calcd for $C_6H_9N_3O_3$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.31; H, 5.37; N, 24.41.

4.5.2. Compound 16b. White powder from ethyl acetate/petroleum ether (40–60°C); mp 158–160°C; IR: ν_{max} 3200, 1730, 1640, 1570 cm^{-1}; δ_H (DMSO-d_6) 2.14 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 7.12 (1H, t, *J*=7.6 Hz, aromatic), 7.37 (2H, t, *J*=7.6 Hz, aromatic), 7.54 (2H, d, *J*=7.6 Hz, aromatic), 11.20 (1H, s, NH, D_2O exch.), 12.01 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 9.0 (q), 60.2 (q), 119.9 (d), 123.9 (d), 126.6 (s), 129.1 (d), 136.9 (s), 141.3 (s), 146.3 (s), 157.5 (s); MS: *m*/*z* (%) 247 (14) [M$^+$], 128 (100). Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.41; H, 5.28; N, 16.78.

4.5.3. Compound 16c. Yellow powder from ethyl acetate/petroleum ether (40–60°C); mp 119–121°C; IR: ν_{max} 3440, 1760, 1690, 1590 cm^{-1}; δ_H (DMSO-d_6) 1.47 (9H, s, CO_2*t*-Bu), 2.04 (3H, s, CH_3), 3.63 (3H, s, OCH_3), 10.31 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 9.5 (q), 27.6 (q), 60.0 (q), 83.6 (s), 127.8 (s), 143.0 (s), 146.7 (s), 157.9 (s); MS: *m*/*z* (%) 228 (11) [M$^+$], 128 (100). Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.68; H, 7.18; N, 12.21.

4.6. General procedure for the synthesis of 2-thiazolin-4-ones 18a–c

To polymer-bound 1,2-diaza-1,3-butadienes **5f**–**h** in MeOH (7 ml) thiobenzamide (10 equiv.) was added, under magnetic stirring. The reaction was allowed to stand at room temperature for 2–3 h obtaining **18a**–**c** in solution (>11–42%). The resin was washed with MeOH, THF and DCM (3×5 ml) and the solvent was removed in vacuo and the 2-thiazolin-4-ones **18a**–**c** were purified by chromatogaphy separation on a silica gel column (elution with ethyl acetate–cyclohexane mixtures). The final products **18a**–**c** were compared with authentic specimens by means of chromatographic and spectroscopic techniques (TLC, IR, NMR, MS).[16]

4.6.1. Compound 18a. Orange powder from methanol; mp 173–174°C; IR: ν_{max} 3300, 3150, 1700, 1680, 1650, 1610, 1560 cm^{-1}; δ_H (DMSO-d_6) 2.27 (3H, s, CH_3), 6.27 (2H, br s, NH_2, D_2O exch.), 7.47–7.50 (3H, m, aromatic), 7.86–7.90 (2H, m, aromatic), 9.30 (1H, br s, NH, D_2O exch.), 11.68 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 15.8 (q), 107.0 (s), 125.9 (d), 129.4 (d), 131.3 (d), 133.0 (s), 147.0 (s), 153.5 (s), 163.1 (s), 164.6 (s); MS: *m*/*z* (%) 276 (30) [M$^+$], 232 (100). Anal. Calcd for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 20.28. Found: C, 52.22; H, 4.42; N, 20.32.

4.6.2. Compound 18b. Yellow powder from methanol; mp 188–189°C; IR: ν_{max} 3360, 3200, 1685, 1675, 1600, 1590 cm^{-1}; δ_H (DMSO-d_6) 2.34 (3H, s, CH_3), 7.00 (1H, t, *J*=7.6 Hz, aromatic), 7.30 (2H, t, *J*=7.6 Hz, aromatic), 7.50–7.58 (5H, m, aromatic), 7.91–7.94 (2H, m, aromatic), 8.65 (1H, s, NH, D_2O exch.), 9.68 (1H, s, NH, D_2O exch.), 11.79 (1H, s, NH, D_2O exch.); δ_C (DMSO-d_6) 15.5 (q), 107.8 (s), 119.6 (d), 123.0 (d), 126.3 (d), 129.4 (d), 130.0 (d), 131.5 (d), 133.4 (s), 139.7 (s), 145.7 (s), 153.7 (s), 162.9 (s), 164.0 (s); MS: *m*/*z* (%) 352 (50) [M$^+$], 259 (100). Anal. Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.42; H, 4.52; N, 15.82.

4.6.3. Compound 18c. Yellow powder from methanol; mp 169–170°C; IR: ν_{max} 3200, 3140, 1690, 1680, 1590 cm^{-1}; δ_H (DMSO-d_6) 1.47 (9H, s, CO_2*t*-Bu), 2.28 (3H, s, CH_3), 7.48–7.53 (3H, m, aromatic), 7.89–7.95 (2H, m, aromatic), 10.04 (1H, s, NH, D_2O exch.), 11.95 (1H, br s, NH, D_2O exch.); δ_C (DMSO-d_6) 16.5 (q), 28.0 (q), 80.0 (s), 104.5 (s), 125.8 (d), 129.3 (d), 131.1 (d), 132.6 (s), 150.4 (s), 153.3 (s), 165.4 (s), 166.4 (s); MS: *m*/*z* (%) 333 (20) [M$^+$], 277 (100). Anal. Calcd for $C_{16}H_{19}N_3O_3S$: C, 57.64; H, 5.74; N, 12.60. Found: C, 57.52; H, 5.82; N, 12.72.

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References

1. (a) Gordon, E. M.; Kerwin, Jr., J. F. *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Wiley: Weinheim, 1998. (b) Terrett, N. K. *Combinatorial Chemistry*; Oxford University: Oxford, 1998. (c) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817–827. (d) Jung, G. *Combinatorial Chemistry*; Wiley: Weinheim, 1999. (e) James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946. (f) Dörner, B.; Steinauer, R.; White, P. *Chimia* **1999**, *53*, 11–17. (g) Seneci, P. *Solid Phase Synthesis and Combinatorial Technologies*; Wiley: New York, 2000. (h) Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*; Wiley: Weinheim, 2000.
2. (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527–4554. (b) Hermkens, P. H. H.; Ottenheijm, H. J. C.; Rees, D. *Tetrahedron* **1997**, *53*, 5643–5678. (c) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385–15443.
3. (a) Tietze, L. F.; Steinmetz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 651–652. (b) Tietze, L. F.; Steinmetz, A. *Synlett* **1996**, 667–668. (c) Tietze, L. F.; Hippe, T.; Steinmetz, A. *Synlett* **1996**, 1043–1044. (d) Tietze, L. F.; Steinmetz, A.; Balkenhohl, F. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1303–1306. (e) Tietze, L. F.; Hippe, T.; Steinmetz, A. *Chem. Commun.* **1998**, 793–794.
4. (a) Attanasi, O. A.; Caglioti, L. *Org. Prep. Proc. Int.* **1986**, *18*, 299–327. (b) Attanasi, O. A.; Filippone, P. *Synlett* **1997**, 1128–1140.
5. (a) Banert, K. *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Rome, 2000; Vol. 3, p. 1, Chapter 1. (b) Polanc, S. *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Società Chimica Italiana: Rome, 2000; Vol. 3, Chapter 2 and references cited therein.
6. (a) Ferguson, G.; Lough, A. J.; Mackay, D.; Weeratunga, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3361–3369. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Molina, M. M.; Palacios, J. C.; Sánchez, J. B. *Tetrahedron Lett.* **1991**, *32*,

2513–2516. (c). Gilchrist, T. L.; Lemos, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1391–1395. (d) South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *J. Org. Chem.* **1996**, *61*, 8921–8934.

7. (a) Arcadi, A.; Attanasi, O. A.; De Crescentini, L.; Rossi, E. *Tetrahedron Lett.* **1997**, *38*, 2329–2332. (b) Attanasi, O. A.; Filippone, P.; Fiorucci, C. *Tetrahedron* **1997**, *53*, 1467–1480. (c) Attanasi, O. A.; De Crescentini, L.; Foresti, E.; Gatti, G.; Giorgi, R.; Perrulli, F. R.; Santeusanio, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1829–1835. (d) Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Mantellini, F. *Synlett* **1997**, 1361–1362. (e) Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Foresti, E.; Mantellini, F. *J. Org. Chem.* **1998**, *63*, 9880–9887. (f) Arcadi, A.; Attanasi, O. A.; Guidi, B.; Rossi, E.; Santeusanio, S. *Chem. Lett.* **1999**, 59–60. (g) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Synlett* **1999**, 339–341. (h) Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Mantellini, F. *Tetrahedron Lett.* **1999**, *40*, 3891–3894. (i) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Guidi, B.; Perrulli, F. R.; Santeusanio, S. *Synlett* **1999**, 1367–1370. (j) Arcadi, A.; Attanasi, O. A.; Guidi, B.; Rossi, E.; Santeusanio, S. *Eur. J. Org. Chem.* **1999**, 3117–3126. (k) Attanasi, O. A.; Filippone, P.; Foresti, E.; Guidi, B.; Santeusanio, S. *Tetrahedron* **1999**, *55*, 13423–13444.
8. Attanasi, O. A.; Filippone, P.; Guidi, B.; Hippe, T.; Mantellini, F.; Tietze, L. F. *Tetrahedron Lett.* **1999**, *40*, 9277–9280.
9. Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713–1718.
10. (a) Visweswariah, S.; Prakash, G.; Bhushan, V.; Chandrasekaran, S. *Synthesis* **1982**, 309–310. (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Serra-Zanetti, F. *J. Heterocycl. Chem.* **1985**, *22*, 1341–1343. (c) Attanasi, O. A.; Filippone, P.; Guerra, P.; Serra-Zanetti, F. *Synth. Commun.* **1987**, *17*, 555–561. (d) Attanasi, O. A.; Grossi, M.; Mei, A.; Serra-Zanetti, F. *Org. Prep. Proc. Int.* **1988**, *20*, 405–408. (e) Dauben, W. G.; Warshawsky, A. M. *Synth. Commun.* **1988**, *18*, 1323–1326. (f) Jacques, J.; Marquet, A. *Org. Synth. Coll.* **1988**, *6*, 175. (g) Attanasi, O. A.; Filippone, P.; Guidi, B.; Perrulli, F. R.; Santeusanio, S. *Heterocycles* **1999**, *51*, 2423–2430.
11. Attanasi, O. A.; Filippone, P.; Mei, A. *Tetrahedron* **1992**, *48*, 1707–1714.
12. Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *49*, 9177–9180.
13. Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 671–672.
14. Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 873–874.
15. Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Foresti, E.; Galeazzi, R.; Ghiviriga, I.; Katritzky, A. R. *Tetrahedron* **1997**, *53*, 5617–5640.
16. Attanasi, O. A.; De Crescentini, L.; Foresti, E.; Galarini, R.; Santeusanio, S.; Serra-Zanetti, F. *Synthesis* **1995**, 1397–1400.