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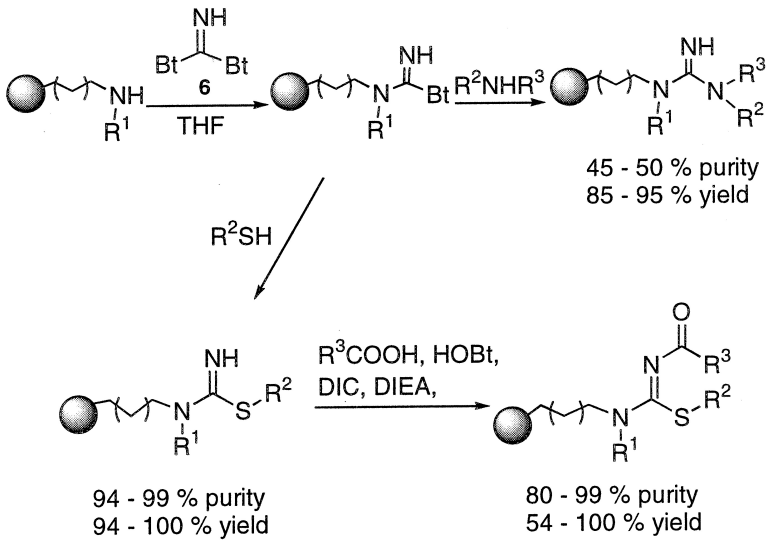

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Versatile Solid-Phase Synthesis of *S*-Arylisothioureas

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Resin-bound amines **4a**−**m** condense with di(benzotriazol-1-yl)methanimine **6** to give 1*H*-benzotriazole-1-carboximidamide resins **7a**−**m**, which subsequently react with thiols **9a′**−**g′** followed by cleavage affording nonprotected isothioureas **1aa′**−**mg′** in high yields and with good purities. Analogous reactions with secondary amines activated with EtMgBr lead to guanidines **2a**,**b**,**e**−**g** in moderate yields. Resin-bound isothioureas **1** are converted by acyl chlorides or carboxylic acids into acyl derivatives **12a**−**n** in high yields and with good purities.

Introduction

Recently, nitric oxide has been identified as an important and unique mediator of diverse physiological processes; thus, NO generated from endothelial cells plays a critical role in the regulation of blood pressure by controlling the dilatation of blood vessels.[1] In activated macrophages, NO acts as a cytostatic and cytotoxic agent and thus is an important part of the host defense system. NO is also thought to act as a messenger molecule in the brain and a neurotransmitter in the peripheral nervous system.[1]

Isothioureas are potent and relatively specific inhibitors of inducible nitric oxide synthase,[1−4] potent and specific fibrinogen receptor antagonist and antivirals for AIDS.[5] Isothioureas were also evaluated for acaricidical activity[6] and as selective herbicides in regard to plantation crops such as sugarcane, coffee, citrus fruits, mangoes, and the like.[7]

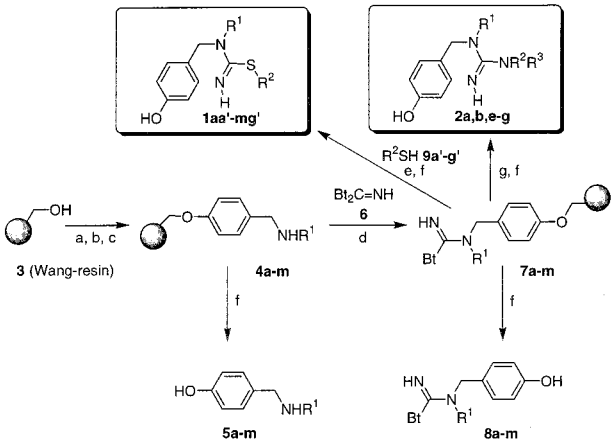
The growing application of combinatorial organic synthesis on solid phase supports[8,9] is reflected in the rapidly increasing range of reaction types and strategies utilized. Following our recent solution-phase preparation of polysubstituted guanidines and isothioureas using di(1*H*-benzotriazolyl)methanimine **6** as a new guanidylating agent,[10] we now report the successful adaptation of this methodology to the solid-phase synthesis of *S*-aryl-*N*,*N*-dialkylisothioureas **1** and some tri- and tetra-substituted guanidines **2**.

Results and Discussion

The overall synthetic strategy for the synthesis of isothioureas **1** and guanidines **2** is outlined in Scheme 1.

We selected Wang resin **3** for the elaboration of our library because of the ease of cleavage of the linker from this support with trifluoroacetic acid (TFA). Resin-bound amines **4a**−**m** were obtained in a three-step procedure involving the known[11a] conversion of the resin **3** to the brominated resin followed by the nucleophilic substitution with 4-hydroxybenzaldehyde in the presence of potassium *tert*-butoxide[11b] and standard reductive amination protocol in the presence of amines and sodium triacetoxyborohydride.[12] Resin-bound amines **4a**−**m** were cleaved, and the corresponding free amines **5a**−**m** were obtained and characterized by ^{1}H NMR and evaporative light-scattering detector (ELSD) LC−MS analysis (Table 1).

Scheme 1[a]



[a] (a) Ph_3PBr_2, DCM, room temp; (b) 4-HO−C_6H_4CHO, *t*-BuOK, DMA, 80 °C, 4 h, 40 °C, 15 h; (c) R^1NH_2, $NaBH(OAc)_3$, DCE, room temp; (d) THF, 7 h, room temp; (e) THF, room temp, 12−14 h; (f) 20% TFA/DCM, 0.5 h; (g) R^2R^3NH/EtMgBr, THF, room temp.

In most cases amines **5** (as TFA salts) were obtained in almost quantitative yields when reductive aminations of 12−24 h were used to make the precursors **4a**−**m**. The only exception was sterically hindered *neo*-Am derivative **5d**, which required prolonged treatment (36 h) in the reductive amination for a quantitative yield. Decreasing the reaction time to 12 h did not affect the yield and purity of amines **5g**,**h**,**j**,**l**,**m** bearing such weakly electron-withdrawing substituents R^1 as Bn, Ph_2CHCH_2, and $Ar(CH_2)_2$. In contrast, unreacted 4-hydroxybenzaldehyde was detected in cleaved

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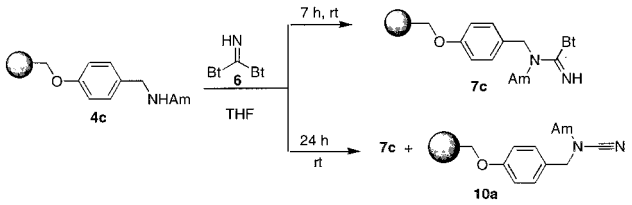
Table 1. Reaction Times for the Preparation of Resins **4a**−**m** and Yields and Purities of TFA Salts of Respective Amines **5a**−**m**

Compound	R^1	Reaction Time, h	Yield, %	^{1}H NMR purity, %	LC-MS purity, %	Additional Treatment, h	Final ^{1}H NMR purity, %
5a	Bu	12	94	75	95	12	99
5b	*i*-Bu	24	98	95			
5c	Am	24	~100		99		
5d	*neo*-Am	24	96	80	90	12	99
5e	$EtO(CH_2)_2$	12	98	80	85	12	99
5f	$MeO(CH_2)_3$	24	99	99			
5g	Bn	12	~100	99	99		
5h	$Ph(CH_2)_2$	12	97	90	95		
5i	$Ph(CH_2)_3$	24	99	98			
5j	Ph_2CHCH_2	12	~100	95	99		
5k	$Me_2N(CH_2)_2$	24	98[a]	98			
5l		12	~100[a]	95	95		
5m		12	97[a]	95	95		

[a] Calculated for double TFA salts.

Scheme 2



samples of the Bu-**5a** and $EtO(CH_2)_2$-**5e** substituted amines after 12 h. An additional treatment over 12 h allows compounds **5a,e** to be prepared in quantitative yields (Table 1).

Condensations of resin-bound amines **4a**−**m** with a suspension of di(1*H*-benzotriazolyl)methanimine **6** in THF over 7 h followed our previously developed solution-phase protocol.[10] According to the gel-phase (GP) ^{13}C NMR spectra of resin **7c** and according to both the LC−MS and ^{1}H NMR analyses of the cleaved sample, the reaction conditions afforded almost quantitative yield of the desired compound **8c**. As observed by GP ^{13}C NMR, extension of the reaction time to 24 h caused resin **7c** to be contaminated with cyanamide resin **10a** (Scheme 2).

We believe that fast addition of di(1*H*-benzotriazolyl)-methanimine **6** to resin **4a** was followed by the subsequent loss of a molecule of benzotriazole, resulting in the formation of the cyanamide resin **10a**. This hypothesis was confirmed by extension of the reaction time to 48 and 120 h and an increase in the temperature. While GP ^{13}C NMR of the resins obtained showed that the desired carboximidamide resin **7c** was still the major component of the mixtures after 2 days at room temperature, cyanamide resin **10a** became the main product after 5 days at the same temperature and was obtained as the sole pure compound after reflux for an additional 24 h. By monitoring the loss of benzotriazole (TLC control of the solutions) during the condensations, we determined that this side reaction could be avoided by performing the addition for only 5−6 h. Following this procedure, the expected 1*H*-benzotriazole-1-carboximidamide resins **7a**−**m** were obtained in high yields and with good purities. However, attempts to carry out an analogous condensation with a resin-bound *N*-arylamine failed, probably because of the reduced nucleophilicity of aromatic amines compared to the aliphatic derivatives **4a**−**m**.

To characterize the influence of a substituent R^1 in the amino group of **7** and of R^2 in thiol **9** on the formation of isothioureas, we prepared a trial library of isothioureas **1aa′**−**mi′** using a set of 13 para-substituted resins **7a**−**m**, nine aromatic thiols **9a′**−**i′**, three heterocyclic thiols **9j′**−**l′**, and benzylthiol **9m′**. After removal of all TFA, each cleaved sample was weighed out on precision balances to determine the yield and was characterized with both ^{1}H NMR and LC−MS analyses (Scheme 1, Table 2).

For most combinations of the substituents used (R^1 = Bu, *i*-Bu, Am, *neo*-Am, $EtO(CH_2)_2$, $MeO(CH_2)_3$, Bn, $C_6H_5(CH_2)_2$, $C_6H_5(CH_2)_3$, $(C_6H_5)_2CHCH_2$, 2-(2-pyridyl)ethyl; R^2 = Ph, 2-Me−C_6H_4, 4-Me−C_6H_4, 4-Cl−C_6H_4, 4-MeO−C_6H_4, 2-$C_{10}H_7$, 2-benzothienyl, 4-NO_2−C_6H_4, 2-NH_2−C_6H_4) the corresponding isothioureas **1** were obtained in very good yields and with high purities (Table 2). Nevertheless, some limitations were recognized for usage of both R^1 and R^2 groups.

Table 2. Yields and LC−MS Purities of Isothioureas **1aa′**−**mg′**[a]

	R¹ \ R²	a′ Ph	b′ 2-Me-C_6H_4	c′ 4-Me-C_6H_4	d′ 4-Cl-C_6H_4	e′ 4-MeO-C_6H_4	f′ 2-$C_{10}H_7$	g′ 2-C_8H_5S
a	Bu			~100/95				
b	*i*-Bu	90/99	89/95	~100/99	93/95	88/95	85/95	~100/85
c	Am	87/99			~100/95			~100/90
d	*Neo*-Am	70/95	85/95	~100/90	86/97	83/95	82/90	83/85
e	$EtO(CH_2)_2$			96/99				
f	$MeO(CH_2)_3$	80/90	78/95	~100/97	83/90	79/95	78/90	99/85
g	Bn			~100/95[b]				
h	$Ph(CH_2)_2$			~100/95[b]				
i	$Ph(CH_2)_3$	86/95	98/95	~100/98	88/95	80/95	89/90	92/85
j	Ph_2CHCH_2			~100/95				
k	$Me_2N(CH_2)_2$	73/50	80/40	N/d	N/d	N/d	N/d	
l				~100/95				
m				N/d				

[a] N/d = product is not detected. [b] Determined by ^{1}H NMR.

Desired isothioureas **1k**,**m** were obtained not at all or in very low yields from resin-bound amines **4k**,**m**, bearing the nitrogen-containing substituents 2-dimethylaminoethyl or 2-(4-pyridyl)ethyl. In contrast, 2-(2-pyridyl)ethyl-substituted compound **1lc′** was prepared quantitatively with 95% purity. The reason for this behavior is not clear. Thiols with reduced nucleophilicity caused by electronic effects (as in 4-nitrothiophenol **9h′**), thiols with intramolecular coordination (as in 2-aminothiophenol **9i′**), and heteroaromatic thiols **9j′**−**l′** existing predominantly as thione tautomers[13] did not formed the desired isothioureas even in low yields. The yield of benzylisothiourea **1bm′** (40%) was strongly reduced in comparison with aromatic derivatives.

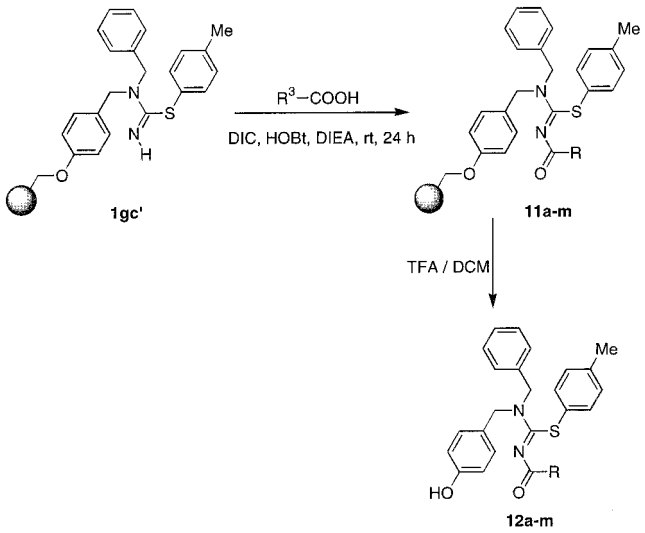
Since 1*H*-benzotriazole-1-carboximidamides resins **7** are sensitive toward an increase in the temperature, condensations of resins **7b**,**c** with various amines were performed at 20 °C for 24 h in the presence of equimolar amounts of ethylmagnesium bromide as an activating agent (Scheme 1). After the usual cleavage protocol (20% solutions of TFA in dry CH_2Cl_2 for 1 h), the guanidines **2a**−**g** obtained were characterized as their TFA salts by LC−MS analysis. Two distinct signals were observed in the LC−MS spectra, corresponding to the desired products **2a**,**b**,**e**−**g** and unreacted starting materials **7b**,**c**. Extension of the reaction time does not affect the yields and purities of the guanidine products **2a**,**b**,**e**−**g** (Scheme 1, Table 3).

To increase the diversity of isothioureas **1**, we tested their acylations with toluoyl and propionyl chlorides in the presence of a base (DMAP) and also used the corresponding carboxylic acids under the following conditions: (i) DIC (10 equiv), HOBT (10 equiv), DIEA (10 equiv), carboxylic acid (10 equiv), DCM/DMF (1:1), 24 h, 20 °C; (ii) HBTU (10 equiv), DMAP (10 equiv), DIEA (10 equiv), carboxylic acid

Table 3. Condensations of Amines with Resins **7a,b** in the Presence of Ethylmagnesium bromide

entry	resin	amine	product	LC−MS purity of **2** (%)
1	**7b**	piperidine	**2a**	40
2	**7b**	4-toluidine	**2b**	45
3	**7b**	ethyl nipecotate	**2c**	complex mixture
4	**7b**	4-nitroaniline	**2d**	complex mixture
5	**7c**	tetrahydroisoquinoline	**2e**	~41
6	**7c**	morpholine	**2f**	~40
7	**7c**	anisidine	**2g**	49

Scheme 3



(10 equiv), DCM/DMF (1:1), 48 h, 20 °C. 3-Acylisothioureas **12a**−**m** were obtained in 54−100% yields and with purities of 80−99% according to ^{1}H NMR (Scheme 3, Table 4). In contrast, an attempt to acylate resin-bound isothioureas using

Table 4. Preparation of *N*-Acyl-*S*-arylisothioureas **12a**−**n**

Entry	Compound **12**	$R^3C{=}O$	^{1}H NMR Purity, %	LC-MS Purity, %	Yield, %
1	**12a**		80	80	54
2	**12b**		95	100	95
3	**12c**		95	100	100
4	**12d**		80	95	66
5	**12e**		90	10	55
6	**12f**		95	20	91
7	**12g**		95	2	94
8	**12h**		95	10	100
9	**12i**		99	100	89
10	**12j**		100	95	79
11	**12k**		90	5	>100
12	**12l**		100	80	82
13	**12m**		95	99	69
14	**12n**	$CH_3C{=}O$	90	1	92

condition iii—DIC (10 equiv), DMAP (10 equiv), DIEA (10 equiv), a carboxylic acid (10 equiv), DCM/DMF (1:1), 24 h, 20 °C—gave no positive result. Investigation of compounds **12a**−**m** by LC−MS showed purities of 80−100% in most of the cases (Table 4). However, 3-alkylacyl-substituted isothioureas **12e,f,h,k,n** and 2,5-difluorobenzoyl derivative **12g** were found to be unstable at storage. This conclusion was confirmed by comparison of ^{1}H NMR spectra of freshly cleaved samples of **12e,f,g,h,k,n** with those obtained after 15 days of storage in acetone-d_6 solution at ambient temperature.

Conclusions

The preparation of resin-bound 1*H*-benzotriazole-1-carboximidamides **7a**−**m** by the reaction of resin-bound amines **4a**−**m** with a solution of di(benzotriazol-1-yl)methanimine **6** for a short reaction time has been described. The condensation of the obtained resins **7a**−**m** with aromatic thiols followed by the appropriate cleavage affords desired isothioureas **1aa′**−**mg′** in high yields and with good purities. Condensation of resins **7b**,**c** with amines in the presence of ethylmagnesium bromide affords guanidines **2a**,**b**,**e**−**g** in moderate yields.

Experimental Section

General Methods. ^{1}H, ^{13}C, and GP ^{13}C NMR spectra were recorded on a 300 MHz NMR spectrometer (300, 75, and 75 MHz, respectively) using $CDCl_3$, DMSO-d_6, and acetone-d_6 as solvents. HPLC purity of the crude materials (confirmed by ^{1}H NMR) was measured on an HP 1050 series chromatograph using a YMC-Pack Pro C18 column (75 mm × 4.6 mm) with a gradient of 5% AcCN/H_2O to 90% AcCN in 5.4 min, a flow rate of 2.64 mL/min, and UV detection at 254 nm. The results were confirmed by mass spectra (ESI). Tetrahydrofuran (THF) was distilled under nitrogen immediately before use from sodium/benzophenone. All other reagents and solvents were obtained from commercial sources and were used without purification.

Procedure for the Preparation of the Resin-Bound Aldehyde. Brominated Wang resin was prepared following a described protocol.[9] A solution of 4-hydroxybenzaldehyde (4.58 g, 37.5 mmol) in dry DMA (150 mL) was reacted with potassium *tert*-butoxide (4.21 g, 37.5 mmol) under an inert atmosphere for 10 min. The solution obtained was added to the brominated resin (2.4 g, 0.87−1.3 mmol/g), and the mixture was heated to 70 °C for 4 h before being allowed to react for an additional 15 h at 40 °C. After removal of the solution, the resin was washed and dried under vacuum for 24 h. A standard washing procedure was used as follows (5 mL of solvent was used for each 100 mg of a resin): DMA × 2, THF × 2, THF/H_2O × 2, THF × 4, DCM × 2, MeOH × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 4. The obtained resin was cleaved with 20% TFA solution in CH_2Cl_2 for 30 min, and the isolated residue was characterized by the ^{1}H NMR, ^{13}C NMR, and LC−MS spectra.

Procedure for the Preparation of Resins 4a−**m.** The resin-bound aldehyde, prepared as described above (0.1 g, loading of 0.87−1.3 mmol/g), was placed in dichloroethane (20 mL), and an appropriate amine (l0 equiv) was added to the solvent followed by sodium triacetoxyborohydride (l0 equiv). The reaction mixture was shaken overnight (for ∼12−14 h). After that the solution was removed, and the resin was washed. The washing sequence was used as follows (5 mL of a solvent was used for each 100 mg of a resin): THF × 4, THF/H_2O (1/1) × 2, THF × 2, THF/H_2O (1/1) × 2, H_2O × 2, THF × 4, DCM × 2, THF × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 4. After being washed, the resin was dried in a vacuum for 15 h. Cleavage of **4a**−**m** gave amines **5a**−**m** as their TFA salts.

General Procedure for the Preparation of Resins 7a−**m.** Resin **4** (loading of 0.87−1.3 mmol/g) was placed in a hot solution of bis(benzotriazolyl)methanimine **6** (10 equiv, concentration of 0.25 mmol/mL) in THF and shaken for 5−6 h at room temperature. After 6 h the solution was removed and the resin was washed and dried. The washing procedure was used as follows (∼5 mL of a solvent was used for each 100 mg of a resin): THF × 4, DCM × 2, THF × 2, DCM × 2, THF × 2, DCM × 4, MeOH × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 4.

After being washed, the resin was dried in a vacuum for 15 h.

General Procedure for the Preparation of Compounds 1aa′−**1 mg′.** Resin **7** was preswollen in dry THF, and an appropriate arylthiol **9** was added. The reaction mixture was shaken for 12−14 h at room temperature. Then the reaction solution was evacuated and the resin was washed and dried for 15 h. The washing sequence was used as follows (5 mL of a solvent was used for each 100 mg of a resin): THF ×

4, DCM × 4, THF × 4, DCM × 2, THF × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 4. Cleavage of the resin with 20% TFA in DCM gave the desired compounds **1aa′**−**1 mg′** as their TFA salts.

General Procedure for the Preparation of Compounds 12a−**m.** A mixture of HOBT, DIC, and DIEA (10 equiv of an each component, concentration of 0.25 mmol/mL) in DMF was added to resin **1gc′**. An appropriate carboxylic acid (10 equiv) was added, and the mixture obtained was shaken for 24 h. Then the reaction solution was evacuated and the resin was washed and dried for 15 h. The washing sequence is as follows (5 mL of a solvent was used for each 100 mg of a resin): DMF × 2, THF × 4, DCM × 4, THF × 4, DCM × 2, THF × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 4. Cleavage of the resin with 20% TFA in DCM gave the desired compounds **12a**−**n**.

Supporting Information Available. ^{1}H NMR and/or LC−MS data for compounds **5a**−**m** and **1aa′**−**mg′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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