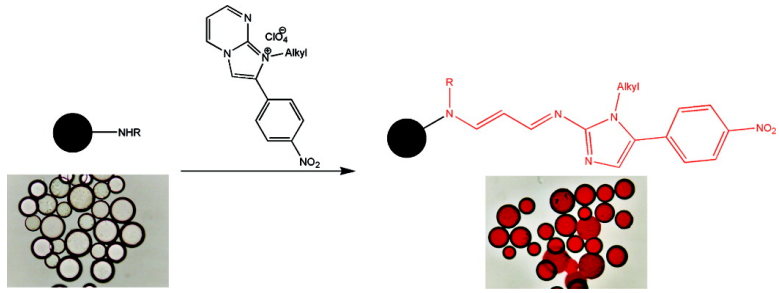
JOURNAL OF combinatorial CHEMISTRY

Article

A New Colorimetric Test for Solid-Phase Amines and Thiols

Stijn Claerhout, Denis S. Ermolat'ev, and Erik V. Van der Eycken

J. Comb. Chem., **2008**, 10 (4), 580-585• DOI: 10.1021/cc800031y • Publication Date (Web): 11 June 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

A New Colorimetric Test for Solid-Phase Amines and Thiols

Stijn Claerhout, Denis S. Ermolat'ev, and Erik V. Van der Eycken*

Laboratory for Organic and Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

Received February 27, 2008

A new, efficient, sensitive, and reliable color test for the visual detection of resin-bound primary and secondary amines is described. The reaction between amines and 1-methyl-2-(4′-nitrophenyl)-imidazo[1,2-*a*]pyrimidinium perchlorate (DESC) provides the "on-bead generated" colored stable intermediate azadiene. The developed protocols allow detection of resin-bound primary amines in the presence of secondary amines. The test can also be used for the detection of resin bound thiols.

Introduction

Solid-phase organic synthesis (SPOS), originally developed by Merrifield[1] for the polymer-supported synthesis of peptides, has now become an important technique for the synthesis of almost any class of organic compounds,[2] especially for the generation of combinatorial libraries[3] and peptides,[4] which are important for drug discovery.[5] In SPOS, it is more difficult to monitor the reaction because the chemical transformations proceed on insoluble resin beads, and, therefore, fast solution-phase analysis methods, such as TLC and LCMS, are not directly applicable for SPOS. Also NMR,[6] IR[7] and electrochemical impedance spectroscopy[8] (EIS) experiments are not straightforward on resin. This makes the monitoring of solid-phase reactions a challenging subject.

A variety of direct (on-bead) and indirect (off-bead) techniques has been developed. Simple colorimetric tests, however, still remain the most convenient way for providing information of the course of solid-phase reactions. A color test, which indicates by visual detection the presence or absence of a functional group, is a simple, practical tool to monitor the completeness of the reaction. The ninhydrin test,[9] originally developed by Kaiser et al. in 1970, was the first colorimetric test for the detection of primary amine and is still widely used in peptide synthesis. Throughout the years a number of new color tests for various functional groups have been reported.[10]

Resin-bound primary or secondary amines are visually detectable with ninhydrin,[9] bromophenol blue,[11] chloranil,[12] 2,4,6-trinitrobenzenesulphonic acid (TNBS),[13] 4-*N*,*N*′-dimethylaminoazobenzene-4′-isothionate[14] (DABITC), 4-nitrophenyl-5-{*N*-ethyl-*N*-[4-(nitrophenyl)azo]phenyl}amino-3-oxapentanoate (NF31),[15] and 2,3-dichloro-5-nitro-1,4-naphthoquinone.[16] Although these number of available color tests useful for solid phase peptide synthesis (SPPS), we believe that there is still a need for reliable and sensitive tests for the visual detection of primary and secondary amines.

Here, we wish to report a novel, simple, fast, and sensitive colorimetric assay for the visual detection of solid-phase bound primary and secondary amines, as well as thiols, using 1-alkyl-2-aryl-imidazo[1,2-*a*]pyrimidinium salts.

Results and Discussion

We have recently reported a new procedure for the synthesis of polysubstituted 2-aminoimidazoles,[17] employing substituted 2-aminopyrimidines and α-bromocarbonyl compounds.[18] The intermediate imidazo[1,2-*a*]pyrimidinium salts, appeared to give a deep color in reaction with primary and secondary amines at room or at slightly elevated temperature. We have synthesized a series of 1-alkyl-2-aryl-imidazo[1,2-*a*]pyrimidinium perchlorates **4a**−**t** from the readily available substituted 2-aminopyrimidines **1** and phenacyl bromides **2** (Scheme 1).

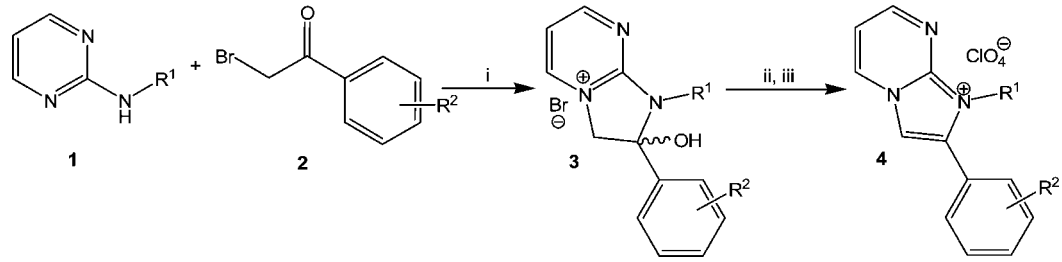
The resulting salts **4a**−**t** were in turn tested for a possible color change upon reaction with resin-bound primary amines (aminomethylated polystyrene resin from Novabiochem; loading 0.5 mmol/g) (Table 1). It appeared that all the salts bearing a *para*-nitro group (R^2) at the phenyl ring gave a red color change of the resin beads (Table 1, entries 6, 14−20). Variation of R^1 did not affect noticeably the coloration (Table 1).

Importantly, 1-alkyl-2-aryl-imidazo[1,2-*a*]pyrimidinium perchlorate salts **4a**−**t** are soluble in common organic solvents, for example, DMF, DMSO, acetonitrile, methanol, and acetone, whereas the corresponding bromides are less soluble and do not give any color upon treatment with resin bound primary amines. All further color tests were performed with 1-methyl-2-(4′-nitrophenyl)-imidazo[1,2-*a*]pyrimidinium perchlorate **4f**, which is forthwith called "DESC".[19] This crystalline reagent can be stored for several months at room temperature without noticeable decomposition. We presume that the strong color that appears upon reaction of DESC with amines, for example, piperidine, is the result of the formation of a conjugated azadiene compound **5**, resulting in a colorant with λ_{max} at 455 and 361 nm. These absorption bands are most probably a result of the intramolecular charge transfer because the presence of a *para*-nitro phenyl group (Scheme 2).[20]

* To whom correspondence should be addressed. E-mail: erik.vandereycken@chem.kuleuven.be.

10.1021/cc800031y CCC: $40.75
Published on Web 06/11/2008

Scheme 1. Synthesis of 1-Alkyl-2-aryl-imidazo[1,2-*a*]pyrimidinium Perchlorates **4**[a]



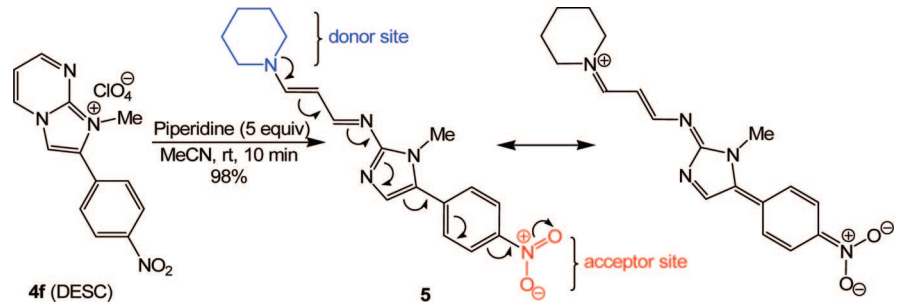
[a] Reagents and conditions: (i) MeCN, 100 °C, MW 150 W, 20 min; (ii) PPA, 140−150 °C, 15−20 min; (iii) 70% $HClO_4$ (10 equiv), H_2O, rt, 15 min.

Table 1. Synthesis and Color Test of 1-Alkyl-2-aryl-imidazo[1,2-*a*]pyrimidinium Perchlorates (**4a**−**t**) with Resin-Bound Primary Amines

entry	compd **3**, **4**	color change[a]	R^1	R^2	yield of **3** (%)[b]	yield of **4** (%)[b]
1	**a**	−	Me	4′-F	69	91
2	**b**	−	Me	4′-Br	88	83
3	**c**	−	Me	4′-Cl	74	94
4	**d**	−	Me	4′-I	71	82
5	**e**	−	Me	4′-MeO	57	80
6 (DESC)	**f**	+	**Me**	**4′-NO_2**	**95**	**89**
7	**g**	−	Me	4′-Me	70	77
8	**h**	−	Me	4′-H	81	78
9	**i**	−	Me	3′,4′-diF	76	95
10	**j**	−	Me	3′-NO_2	64	58
11	**k**	+	Me	4′-MeS	69	64
12	**l**	+	Et	4′-NO_2	89	69
13	**m**	+	Bu	4′-NO_2	83	86
14	**n**	+	Bn	4′-NO_2	85	54
15	**o**	+	homoveratryl	4′-NO_2	65	72
16	**p**	+	*i*-Pr	4′-NO_2	91	89
17	**q**	+	*i*-Bu	4′-NO_2	79	58
18	**r**	+	cyclopropyl	4′-NO_2	62	73
19	**s**	+	cyclohexyl	4′-NO_2	84	59
20	**t**	+	cyclododecyl	4′-NO_2	88	44

[a] A few beads of aminomethylated resin (0.5 mmol/g, Novabiochem) were suspended at rt in the freshly prepared solution of the salt **4a**−**t** (0.01 M) in DMF (100 μL), and the color change was evaluated after 5 min; − stands for a negative test (no color change), and + stands for a positive test. [b] Isolated yields are given.

Scheme 2. Formation of the Azadiene Intermediate **5** upon Reaction of DESC with Piperidine



Thus, having detected a strong coloration for resin bound primary and secondary amines upon treatment with DESC, we have elaborated a standard protocol. For the detection of primary amines the following procedure has been established: a few beads are suspended in 100 μL of a 0.01 M DESC solution in DMF. After they were heated at 60 °C for 5 min, the beads are washed with DMF (3×), MeOH (3×), and DCM (3×). Beads containing deprotected amino groups appear as red to dark orange spheres, while beads containing no free amino groups remain colorless. In most cases, heating is not necessary for the detection of primary amines because the color appears immediately after addition of a solution of DESC. Only for very low concentrations of free primary amines heating is necessary to enhance the sensitivity of the test. The procedure for the detection of secondary amines is slightly different. A few drops of a 20% DIEA solution in DMF are added after the addition of DESC to the resin beads. The solution turns dark after addition of the DIEA, but after they were heated and washed (according to the procedure described for the detection of primary amines), the beads that contained free secondary amino groups are isolated as red or dark orange spheres, while beads not bearing any secondary amino groups, retained their original color. To guarantee the reliability of the DESC test, it is recommended to refresh the DESC solution monthly.

Evaluation of the Sensitivity of the DESC Test toward Solid-Phase-Bound Primary Amines. A series of resin samples of known free amine content was prepared by coupling aminomethylated polystyrene resin (loading 0.5 mmol/g, Novabiochem) with a mixture of Fmoc-Ala and Boc-Ala in various ratios. After selective removal of the Fmoc-protective group, the final beads were obtained with

Table 2. Comparison of the Sensitivity of DESC and TNBS for Primary Amines at Different Loadings

entry	amine content (mol%)	DESC test	TNBS test
1	2		
2	5		
3	10		
4	20		
5	50		
6	100		

a content of 50, 20, 10, 5, and 2 mol% of free resin bound primary amino groups. Subsequently, these different fractions were treated with DESC and TNBS, and the difference in color change was evaluated (Table 2). DESC seemed to be more sensitive, which is especially useful at low concentration levels of free amine content. TNBS gave a reliable result up to 5 mol % (23 μmol/g) of free amine content, whereas DESC is sensitive up to 2 mol % (9 μmol/g).

To further demonstrate the difference in sensitivity between DESC and TNBS, a mixture of completely protected resin (no free amine present) and resin containing 5 mol % of free primary amine was mixed in a 1:1 ratio and treated with the respective reagents (Figure 1). This test clearly shows that DESC gives a distinct color change even at low free amine content (5 mol %, 23 μmol/g) and that a better contrast is obtained compared to TNBS. Other types of resin, such as aminomethylated polystyrene resin (0.2 mmol/g and 0.9 mmol/g loading) and Hypogel (0.9 mmol/g), a resin containing a polyethylene spacer, also turned red upon treatment with DESC clearly indicating that DESC is a reliable color test for primary amines with sensitivity up to 2 mol % (9 μmol/g) of resin bound free primary amine content.

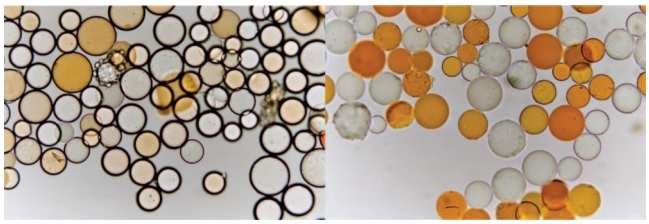


Figure 1. Comparison of the sensitivity of TNBS (left) and DESC (right) for primary amines.

Evaluation of the Sensitivity of the DESC Test toward Solid-Phase-Bound Secondary Amines. As mentioned above, a slightly modified protocol was needed for the detection of secondary amines. A few drops of a 20% DIEA solution in DMF should be added after addition of the DESC solution to the resin and heating for 5 min at 60 °C is necessary. The resin-bound secondary amine was prepared by coupling a backbone amide linker **6** (BAL) with aminomethylated polystyrene resin (0.5 mmol/g, Novabiochem), followed by reductive amination with C-terminal protected phenylalanine, resulting in the formation of resin **8** (Scheme 3).

The resin was thoroughly washed with DMF, DIEA (20% in DMF), dichloromethane, and methanol. The resin-bound secondary amine **8** was then treated with DESC with and without the addition of DIEA (20% in DMF) and heated in both examples. This clearly demonstrated the need for the addition of DIEA for the detection of secondary amines (Figure 2). The protocols for detection of primary and secondary amines using DESC are essentially different, enabling the selective detection of primary amines in the presence of secondary amines. Thus, for example, the course of a reductive amination of a resin-bound primary amine can be followed.

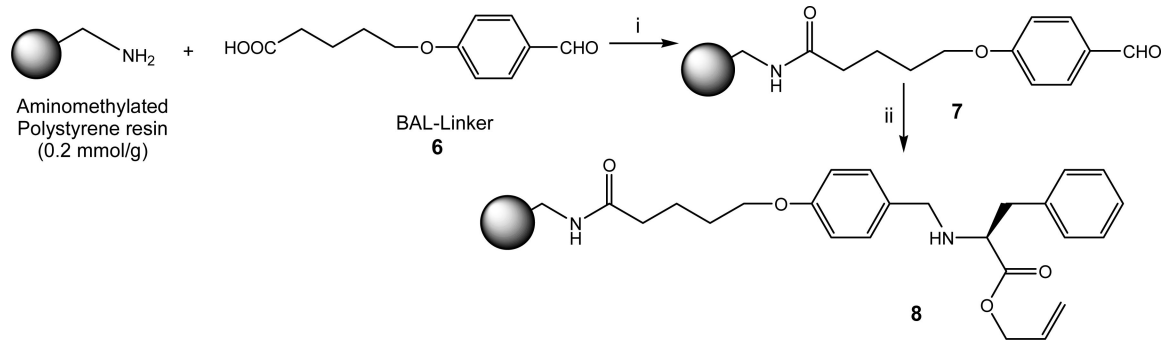
Subsequently, to determine the sensitivity for resin-bound secondary amines, a series of resin samples of known free amine content were prepared by coupling of aminomethylated polystyrene resin (0.5 mmol/g, Novabiochem) with a mixture of Fmoc-Ala and Boc-Ala in varying ratios (Scheme 4). After selective removal of the Fmoc-protective group, the resin was reacted with a backbone amide linker,[21] applying reductive amination conditions. This resulted in the generation of resins with a free amine content of 100, 50, 20, 10, 5, and 2 mol % of secondary amine (Scheme 4, Table 3). The results clearly show that DESC can be used for the detection of secondary amines up to a loading of 2 mol % (9 μmol/g) of free resin-bound secondary amine. A possible application of this test is the detection of the completeness of the coupling of an amino acid to the secondary amine using the BAL strategy,[21] which is known to be a difficult coupling step.

Test with Resin-Bound Thiols. In addition, the DESC test was evaluated for a resin-bound thiol that was derived from a commercially available trityl protected resin (loading 0.88 mmol/g, Novabiochem, Figure 3). Although we did not determine the sensitivity of the test, the very intense dark red color that appeared upon treatment with DESC at room temperature, without addition of base, suggested that this test could be valuable to determine the completeness of reactions where resin-bound thiols are involved (Figure 4).

Conclusions

A new, efficient, sensitive, and reliable test for the visual detection of resin-bound primary and secondary amines was developed based on 1-methyl-2-(4′-nitrophenyl)-imidazo[1,2-*a*]pyrimidinium perchlorate **4f** (DESC). The test can also be used for the detection of resin-bound thiols. The advantage of DESC over previously described solid-phase colorimetric amine tests is the high sensitivity for the detection of secondary and primary amines in a reliable and easy way.

Scheme 3. Synthesis a Resin-Bound Secondary Amine (0.2 mmol/g) via the Backbone Amide Linker (BAL) Strategy[a]



[a] Reagents and conditions: (i) AM PS resin (0.2 mmol/g, Rapp Polymer), DIC (3 equiv), HOBt (3 equiv), BAL linker (3 equiv), MW, 60 °C, 20 min; (ii) H-L-Phe-OAll·HCl (4 equiv), $NaCNBH_3$ (4 equiv), DMF/MeOH (9:1), 16 h.

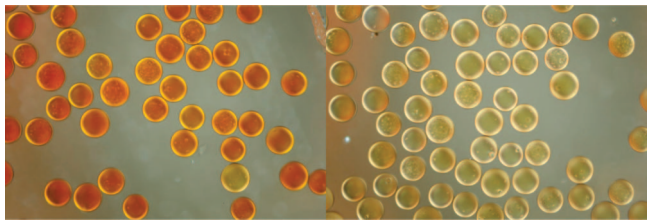


Figure 2. Resin-bound secondary amine treated with DESC and 20% DIEA (left) and only with DESC (right) in DMF solution at 60 °C.

Another advantage of DESC is its ability to follow the conversion of a resin-bound primary amine into a secondary amine as the protocol for detection of primary amines does not cause a color change for secondary amines. DESC is accessible from cheap starting materials and can be prepared on a multigram scale in two steps. A solution of DESC is stable at ambient temperatures and can be used with confidence within one month.

Experimental Section

General Remarks. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 and 400 MHz instruments, using DMSO-d_6, MeOH-d_4, or $CDCl_3$ as solvents. The ^1H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane, using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150−250 °C as required. High resolution EI-mass spectra were performed with a resolution of 10 000. The low-resolution spectra were obtained with a HP5989A MS instrument. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70−230 mesh silicagel (E.M. Merck)) were used. All reagents were purchased from commercial sources and used without further purification. Melting points of the compounds are uncorrected. The aminomethylated polystyrene resin (loading of 0.5 and 0.9 mmol/g) and the trityl-protected thiol resin (0.88 mmol/g) were obtained from Novabiochem. The aminomethylated polystyrene resin (0.2 mmol/g) was obtained from Rapp polymer. A multimode Milestone MicroSYNTH microwave reactor (Laboratory Microwave Systems) was used in the standard configuration as delivered, including proprietary software. Reaction temperatures were monitored by an IR sensor on the outside wall of the reaction vials and fiber optic sensor inside the reaction mixture. All experiments were carried out in sealed microwave process vials (15, 50 mL). After completion of the reaction, the vial was cooled to 25 °C via air jet cooling before it was opened.

Preparation of the DESC Solution. Compound **4f** (35.4 mg) was dissolved in DMF (10 mL, peptide grade, Biosolve) to provide 0.01 M solution of DESC reagent.

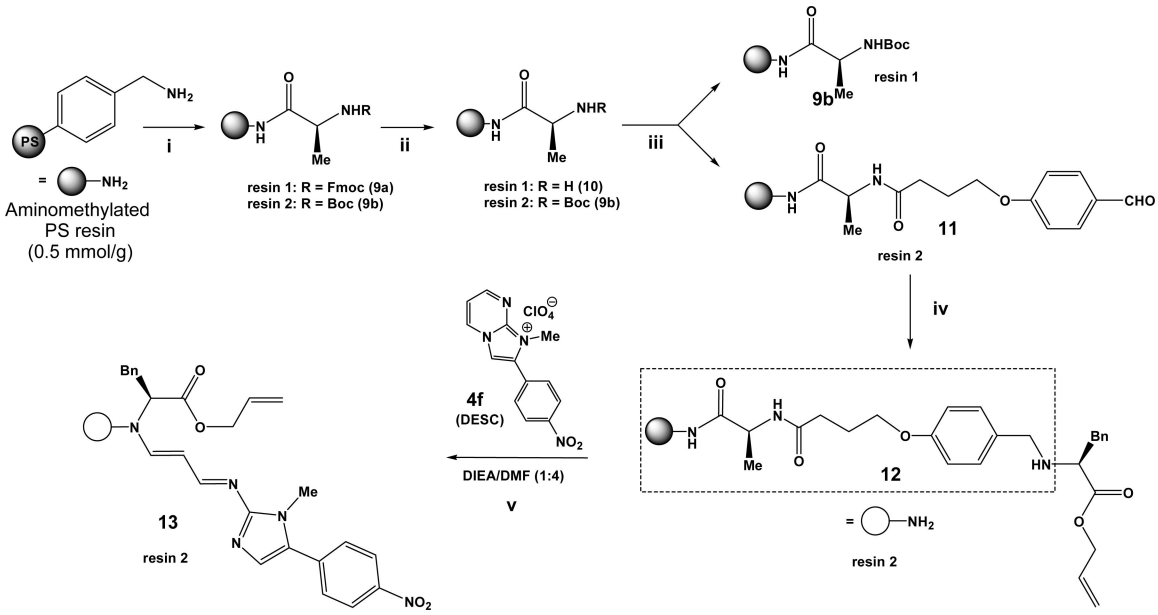
Procedure for the Detection of Resin-Bound Primary Amines with DESC. A few washed resin beads were transferred to a test tube, and the DESC solution (100 μL) was added. The mixture was heated for 5 min at 60 °C and was then diluted with DMF (2 mL) and decanted. The resin beads were washed several times until the supernatant solution was nearly colorless. The color of the resin beads was evaluated with a microscope.

Procedure for the Detection of Resin-Bound Primary Amines with TNBS. To a sample of washed resin beads, a 1 M solution of 2,4,6-trinitrobenzenesulfonic acid (TNBS) in DMF was added. In addition, a solution of *N*,*N*-diisopropylethylamine (DIEA, 20%) in DMF (100 μL) was added. The mixture was left at room temperature for 10 min. The solution was diluted with DMF (2 mL) and decanted. This was repeated several times until the decanted DMF solution was nearly colorless. The color of the resin beads was monitored with a microscope; orange coloration of the beads indicated a positive test.

Procedure for the Detection of Resin-Bound Secondary Amines with DESC. A few washed resin beads were transferred to a test tube, and the DESC solution (100 μL) was added. In addition, a solution of *N*,*N*-diisopropylethylamine (DIEA, 20%) in DMF (100 μL) was added. The solution was heated for 5 min at 60 °C, resulting in a dark coloration of the supernatant liquid. The solution was diluted with DMF (2 mL) and decanted. This was repeated several times until the decanted DMF solution was nearly colorless. The color of the resin beads was evaluated with a microscope. Yellow to red beads indicated the presence of secondary amines.

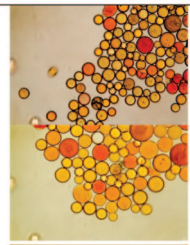
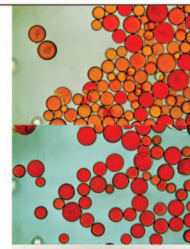
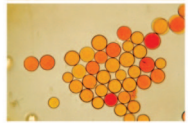
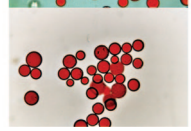
Procedure for the Detection of Resin-Bound Thiols. The procedure for the detection of thiols is similar to that for primary amines. The resin beads (polystyrene thiophenol resin, 0.88 mmol/g, Novabiochem, Figure 3) were transferred to a test tube, and the DESC solution (100 μL) was added. The mixture was heated for 5 min at 60 °C and was then diluted with DMF (2 mL) and decanted. The resin beads

Scheme 4. Synthesis of a Series of Resin-Bound Secondary Amines with a Different Secondary Amine Content[a]



[a] Reagents and conditions: (i) AM resin (0.5 mmol/g), DIC (3 equiv), HOBt (3 equiv), (Boc/Fmoc)Ala-OH (3 equiv), MW, 60 °C, 20 min; (ii) DMF/DIEA (4:1), rt, 20 min. (iii) DIC (3 equiv), HOBt (3 equiv), BAL linker (3 equiv), MW, 60 °C, 20 min; (iv) H-L-Phe-OAll·HCl (4 equiv), $NaCNBH_3$ (equiv), DMF/MeOH (9:1), 16 h; (v) DESC solution, DIEA/DMF (1:4), 60 °C, 10 min.

Table 3. DESC Test at Different Loadings of Secondary Amine

entry	amine content (mol%)	DESC test	entry	amine content (mol%)	DESC test
1	2		4	20	
2	5		5	50	
3	10		6	100	

were washed several times until the supernatant solution was nearly colorless. The color was evaluated with a microscope.

Acknowledgment. The authors thank the IWT (Institute for the Promotion of Innovation by Science and Technology in Flanders) for financial support (SBO-project IWT 040083). D.S.E. is grateful to the University of Leuven for a scholarship. The authors thank Prof. Dr. K. Binnemans for the use of the microscopic camera.

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

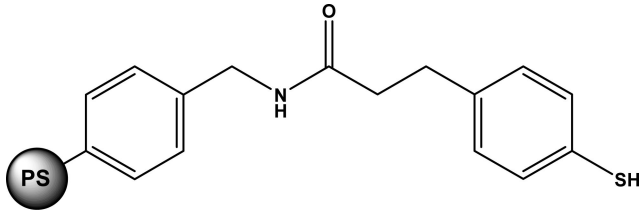


Figure 3. Structure of polystyrene thiophenol resin.

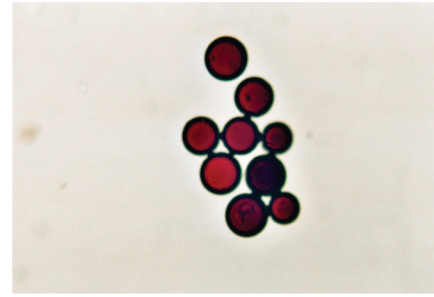


Figure 4. Coloration of resin-bound thiol with DESC.

References and Notes

(1) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.
(2) Guillier, G.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157.
(3) Dolle, R. E.; Le Bourdonnec, B.; Morales, G. A.; Moriarty, K. J.; Salvino, J. M. *J. Comb. Chem.* **2006**, *8*, 597–635. (a) Kaval, N.; Dehaen, W.; Van der Eycken, E. *J. Comb. Chem.* **2005**, *7*, 90–95. (b) Kaval, N.; Singh, B. K.; Ermolat'ev, S. D.; Claerhout, S.; Parmar, V. S.; Van der Eycken, J.; Van der Eycken, E. *J. Comb. Chem.* **2007**, *9*, 446453.
(4) Amblard, M.; Fehrentz, J. A.; Martinez, J.; Subra, G. *Mol. Biotechnol.* **2006**, *33*, 239–254.
(5) Ziegert, R. E.; Toraeng, J.; Knepper, K.; Braese, S. *J. Comb. Chem* **2005**, *7*, 147–169. (a) Sanchez-Martin, R. M.; Mittoo, S.; Bradley, M *Curr. Top. Med. Chem.* **2004**, *4*, 653–669.
(6) Rousselot-Pailey, P.; Ede, N. J.; Lippens, G. *J. Comb. Chem* **2001**, *3*, 559–563. (a) Lippens, G.; Warrass, R.; Wieruszeski, J. M.; Rousselot-Pailley, P; Chessari, G. *Comb Chem. High Throughput Screening* **2001**, *4*, 333–351. (b) Jamieson, C.; Congreve, M. S.; Hewitt, P. R.; Scicinski, J. J.; Ley, S. V. *J. Comb. Chem.* **2001**, *3*, 397–399. (c) Fernandez-Forner, D.; Huerta, J. M.; Ferrer, M.; Casals, G.; Ryder, H.; Giralt, E.; Albericio, F. *Tetrahedron Lett.* **2002**, *43*, 3543–3546. (d) Le Roy, I.; Mouysset, D.; Mignani, S.; Vuilhorgne, M.; Stella, L. *Tetrahedron* **2003**, *59*, 37193727.

(7) Gremlich, H. U. *Biotechnol. Bioeng.* **1999**, *61*, 179–187. (a) Yan, B.; Gremlich, H. U.; Moss, S.; Coppola, G. M.; Sun, Q.; Liu, L. *J. Comb. Chem.* **1999**, *1*, 46–54. (b) Yan, B; Li, W. *J. Org. Chem.* **1997**, *62*, 9354–9357. (c) Mihaichuk, J.; Tompkins, C.; Pieken, W. *Anal. Chem.* **2002**, *74*, 1355–1359.
(8) Hutton, R. S.; Adams, J. P.; Trivedi, H. S. *Analyst* **2003**, *128*, 103–108.
(9) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595–598.
(10) See the articles and references sited herein: (a) Gaggini, F.; Porcheddu, A.; Reginato, G.; Rodriquez, M.; Taddei, M. *J. Comb. Chem* **2004**, *6*, 805–810. (b) Kay, C.; Lorthioir, O. E.; Parr, N. J.; Congreve, M.; McKeown, S. C.; Scicinski, J. J.; Ley, S. V. *Biotechnol. Bioeng.* **2001**, *71*, 110–118.
(11) Krchnak, V.; Vagner, J.; Lebl, M. *Int. J. Pept. Protein Res.* **1988**, *32*, 415–6. (a) Flegel, M; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1990**, 536–538.
(12) Vojkovsky, T. *Pept. Res.* **1995**, *8*, 236–237.
(13) Hancock, W. S.; Battersby, J. E. *Anal. Biochem.* **1976**, *71*, 260–264.
(14) Shah, A.; de Biasi, V.; Camilleri, P.; Rahman, S S. *Anal. Commun.* **1997**, *34*, 325–328.
(15) Madder, A.; Farcy, N.; Hosten, N. G. C.; De Muynck, H.; De Clercq, P. J.; Barry, J.; Davis, A. P. *Eur. J. Org. Chem.* **1999**, *7*, 2787–2791. (a) Van der Plas, S. E.; De Clercq, P. J.; Madder, A. *Tetrahedron Lett.* **2007**, *48*, 2587–2589.
(16) Blackburn, C. *Tetrahedron Lett.* **2005**, *46*, 1405–1409.
(17) Heidler, P.; Link, A. *J. Sul. Chem.* **2005**, *26*, 3–6. (a) Heidler, P; Link, A. *Aus. J. Chem.* **2005**, *58*, 182–187.
(18) Ermolat'ev, S. D.; Babaev, E. V.; Van der Eycken, E. V. *Org. Lett.* **2006**, *8*, 5781–5784.
(19) DESC stands for the inventors names: Denis Ermolat'ev and Stijn Claerhout.
(20) Maiboroda, D. A.; Babaev, E. V.; Goncharenko, L. V. *Khim.—Farm. Zh.* **1998**, *32*, 24–28.
(21) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vagner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441–5452.

CC800031Y