A simple, three-component synthesis of 2-aminothiazoles using trimethylsilyl isothiocyanate

Viktor Golubev, Fedor Zubkov, Mikhail Krasavin

PII: S0040-4039(13)01078-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.06.102
Reference: TETL 43155

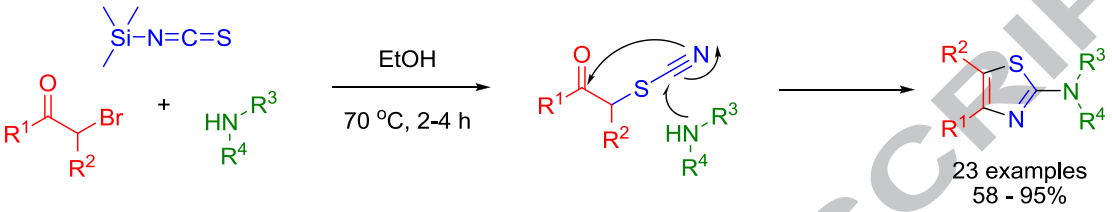
To appear in: *Tetrahedron Letters*

Received Date: 13 May 2013
Revised Date: 9 June 2013
Accepted Date: 21 June 2013

Please cite this article as: Golubev, V., Zubkov, F., Krasavin, M., A simple, three-component synthesis of 2-aminothiazoles using trimethylsilyl isothiocyanate, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.06.102

A simple, three-component synthesis of 2-aminothiazoles using trimethylsilyl isothiocyanate

Viktor Golubev, Fedor Zubkov, Mikhail Krasavin*



A simple, three-component synthesis of 2-aminothiazoles using trimethylsilyl isothiocyanate

Viktor Golubev,[a] Fedor Zubkov,[a] Mikhail Krasavin*[b]

[a] *Peoples' Friendship University of Russia, 6 Miklukho-Maklaya St., Moscow, Russia*

[b] *Eskitis Institute for Drug Discovery, Griffith University, Nathan, Queensland 4111, Australia*

*Corresponding author, e-mail: m.krasavin@griffith.edu.au, phone: +61 7 3735 6041, fax: +61 7 3735 6001.

Abstract: The first multicomponent, solution-phase protocol to prepare privileged 2-aminothiazoles from α-bromocarbonyl compounds and amines (aromatic and aliphatic) using commercially available trimethylsilyl isothiocyanate is described.

Keywords: 2-aminothioazoles, multicomponent reactions, combinatorial chemistry, privileged structures, parallel solution-phase synthesis.

Despite the fact that 2-aminothiazoles have been recently flagged as undesired structural elements for screening library design (arguably, due to their thiourea-like character and tendency to modulate promiscuously multiple biological targets),[1, 2] this heterocyclic core was key in the design of kinase inhibitors (e.g., the marketed cancer drug, dasatinib[3]) and continues to prove its worth in medicinal chemistry practice. Its privileged character is evidenced by 2-aminothiazoles being reported as antiviral,[4] antiprion,[5] anti-inflammatory,[6] antimicrobial,[7] antitubercular[8] and anticancer[9] agents.

Numerous methods to access 4-substituted 2-aminothiazoles **1** have been reported in the literature, with most based on the Hantzsch-type[10] condensation of α-halocarbonyl compounds **2** with various thioureas **3**. The latter can, in turn, be generated from primary and secondary amines using isothiocyanate sources such as (a) benzoyl isothiocyanate (**4**) (with subsequent alkaline hydrolysis),[4] (b) Fmoc-isothiocyanate (**5**) (followed by Fmoc group removal with piperidine),[11] or (c) *tert*-butyl isothiocyanate (**6**), requiring subsequent *tert*-butyl group cleavage under strongly acidic conditions (Scheme 1).[12] However, despite recent developments in the Hantzsch thiazole synthesis (including syntheses under microwave irradiation,[13] in aqueous medium,[14] on solid support,[11] as well as in a flow reactor[15]), there appears to be no convenient protocol that allows conversion of a wide range of α-halocarbonyl compounds and amines (aliphatic and aromatic) into 2-aminothiazoles, in a truly multicomponent format. In this Letter, we report on the development of the first multicomponent solution-phase protocol[16] for the synthesis of 2-aminothioazoles using

commercially available trimethylsilyl isothiocyanate (TMSNCS) along with readily available amine and β-halocarbonyl components.

A few isolated examples of the preparation of 2-aminothiazoles using TMSNCS are available in the patent literature.[17] These typically include stepwise transformation of a secondary aliphatic amine into its *N*-thiocarbamoyl derivative, which in turn is exposed to an α-haloketone to give, upon several hours of reflux in EtOH, the desired 2-aminothiazoles (Scheme 2). This literature precedent prompted us to use TMSNCS to prepare the same heterocycles in a multicomponent format.

Initially, we investigated the possibility of transforming a set of substituted anilines into the respective 2-aminothiazoles. To our delight, simple mixing of the anilines with the respective α-bromocarbonyl compounds **2**, followed by addition of TMSNCS and heating the reaction mixture at 70 °C afforded the target 2-aminothiazoles **1a-n** (Scheme 3, equation 1) in good to excellent yields (Table 1). The latter were isolated as hydrobromide salts by simple filtration.

When we attempted to extend the same approach to primary aliphatic amines, we realized that in order for the desired product to be formed, an equivalent of triethylamine[18] had to be added. This observation appeared to be consistent with the following mechanistic considerations (Scheme 4). When exposed to ethanol, TMSNCS rapidly releases isothiocyanic acid,[19] which could react with the α-bromocarbonyl compound **2** to form the respective thiocyanate **7**.[20] While anilines are certainly capable of scavenging the HBr released when **7** is formed, they are not as basic as aliphatic amines and the amount of unprotonated aniline in the reaction mixture is sufficient to drive the reaction forward, while the 2-aminothiazole product formed becomes a competent scavenger of HBr, thus leading to the complete conversions (*vide supra*). With aliphatic amines, due to their higher basicity, all of the amine present in the reaction mixture is likely to be protonated (as the result of the formation of **7**), and the use of an added organic base is necessary for the reaction to proceed. Apart from this aspect, the general protocol applied to primary aliphatic amines was identical to that used for anilines, leading to the formation of free-base 2-aminothiazoles **1o-s** in good to excellent yields (Scheme 3, equation 2). The same methodology was found to be applicable to secondary aliphatic amines as well, except that the amine (and not TMSNCS) was added last (Scheme 3, equation 3), in order to avoid the formation of α-aminocarbonyl compound **8**. Without such a precaution, **8** was found to form quite rapidly (due to the high nucleophilicity of the secondary amine) which led to a lower yield of the target 2-aminothiazole **1**.

In summary, we developed a convenient multicomponent synthesis of privileged 2-aminothiazoles.[21] The protocol is applicable to a range of aromatic and aliphatic amines, as well as various α-bromocarbonyl substrates. The simplicity of this new 'mix-it-all' methodology is

expected to aid early drug discovery lead generation based on this popular core,[22] possibly leading to thiazole-based biologically active compounds.

2-Aminothiazoles 1 General Procedure: To a solution of α-bromocabonyl compound **2** (1 mmol) in EtOH (2 mL) were added equimolar amounts of the following reagents in the order indicated:

Equation 1 (aromatic amines): amine followed by TMSNCS;

Equation 2 (primary aliphatic amines): amine followed by Et_3N and TMSNCS;

Equation 3(secondary aliphatic amines): TMSNCS followed by Et_3N and amine.

The reaction mixture was heated at 70 °C for 2-4 h and then allowed to cool. The target 2-aminothiazole was filtered off, washed with ice-cold EtOH and air-dried (Equation 1). Alternatively (Equations 2 and 3), the mixture was concentrated *in vacuo* and the target product was isolated by chromatography on silica gel using an appropriate gradient of EtOAc in hexanes.

Acknowledgements

Mikhail Krasavin acknowledges support from Griffith University.

References and notes

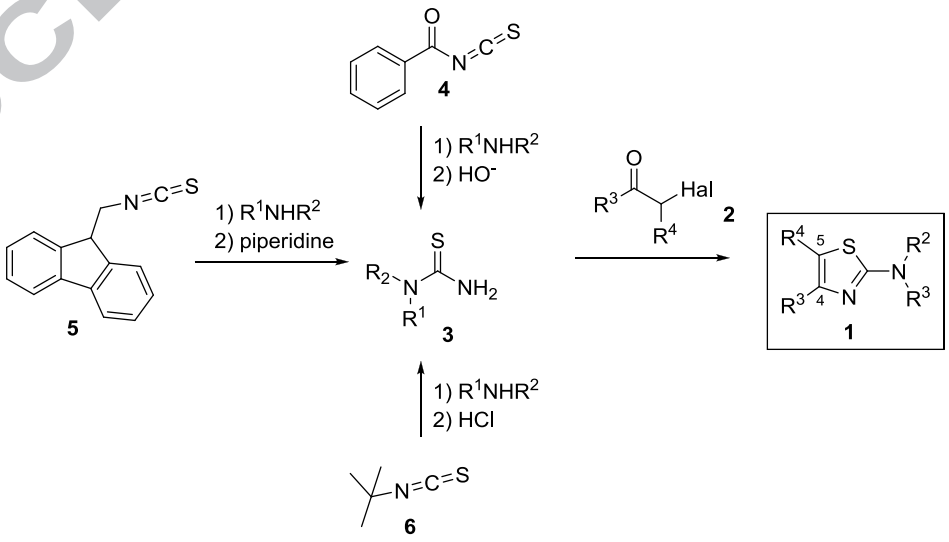
1. Baell, J. B.; Holloway, G. A. *J. Med. Chem.* **2010**, *53*, 2719-2740.
2. Baell, J. B. *J. Chem. Inf. Model.* **2013**, *53*, 39−55.
3. Das, J.; Chen, P.; Norris, D.; Padmanabha, R.; Lin, J.; Moquin, R. V.; Shen, Z.; Cook, L.S.; Doweyko, A. M.; Pitt, S.; Pang, S.; Shen, D. R.; Fang, Q.; de Fex, H. F.; McIntyre, K. W.; Shuster, D. J.; Gillooly, K. M.; Behnia, K.; Schieven, G. L.; Wityak, J.; Barrish, J. C. *J. Med. Chem.* **2006**, *49*, 6819-6832.
4. Liu, R.; Huang, Z.; Murray, M. G.; Guo, X.; Liu, G. *J. Med. Chem.* **2011**, *54*, 5747–5768.
5. Gallardo-Godoy, A.; Gever, J.; Fife, K. L.; Silber, B. M.; Prusiner, S. B.;Renslo, A. R. *J. Med. Chem.* **2011**, *54*, 1010–1021.
6. Suh, J.; Yum, E. K.; Cheon, H. G.; Cho, Y. S. *Chem. Biol. Drug Des*. **2012,** *80*, 90–99.
7. Annadurai, S.; Martinez, R.; Canney, D. J.; Eidem, T.; Dunman, P. M.; Abou-Gharbia, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7719-7725.
8. Roy, K. K.; Singh, S.; Sharma, S. K.; Srivastava, R.; Chaturvedi, V.; Saxena, A. K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5589–5593.
9. Romagnoli, R.; Baraldi, P. G.; Salvador, M. K.; Camacho, M. E.; Preti, D.; Tabrizi, M. A.; Bassetto, M.; Brancale, A.; Hamel, E.; Bortolozzi, R.; Basso, G.; Viola, G. *Bioorg. Med. Chem. Lett.* **2012**, *20*, 7083–7094.
10. Metzger, J. V. Thiazole and its Derivatives, Part 1, John Wiley & Sons, New York, 1979, pp. 166–310.

11. Dadiboyena, S.; Nefzi, A. *Synthesis* **2012**, *44*, 215–218.
12. Bredikhina, Z. A.; Buzykin, B. I.; Kitaev, Yu. P. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1991**, 427-433.
13. Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2006**, *47*, 5171-5172.
14. Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V. *Tetrahedron* **2008**, *64*, 5019-5022.
15. Thompson, C. M.; Poole, J. L.; Cross, J. L.; Akritopoulou-Zanze, I.; Djuric, S. W. *Molecules* **2011**, *16*, 9161-9177.
16. A formal multicomponent synthesis of 2-(alkylamino)thiazole using SiO_2-supported KNCS and Al_2O_3-supported alkylammonium acetates has been reported, see: Aoyama, T.; Murata, S.; Arai, I.; Araki, N.; Takido, T.; Suzuki, Y.; Kodomari, M. *Tetrahedron* **2006**, *62*, 3201-3213. The scope of this methodology, however, appears to be limited and the preparation of the solid-supported reagents is required in advance.
17. (a) Cao, G.-Q.; Chen, J. J.; Dominguez, C.; Reed, A.; Sham, K. K. C.; Thaman, M. C.; Zhang, D.; Herberich, B. J. PCT Int. Appl. WO2005070934A1, 159 pp.; *Chem. Abstr.* **2005**, *143*, 194022; (b) Xiao, D.; Palani, A.; Aslanian, R. G. PCT Int. Appl. WO2010071822A1, 64 pp.; *Chem. Abstr.* **2010**, *153*, 116274; (c) Altman, M. D.; Arrington, K. L.; Burch, J.; Cote, B.; Fournier, J.-F.; Gauthier, J. Y.; Kattar, S.; Knowles, S. L.; Lim, J.; Machacek, M. R.; Northrup, A. B.; Reutershan, M. H.; Robichaud, J. S.; Schell, A. J.; Spencer, K. B. PCT Int. Appl. WO2011075560A1, 77 pp.; *Chem. Abstr.* **2011**, *155*, 123426.
18. Using other bases such as DIPEA or polymer-supported morpholine provided the target 2-aminothiazoles, albeit in somewhat lower yields.
19. Guda, D. R.; Wang, T.; Cho, H. M.; Lee, M. E. *Tetrahedron Lett.* **2012**, *53*, 5238-5242.
20. Renard, P.-Y.; Schwebel, H.; Vayron, P.; Leclerc, E.; Dias, S.; Mioskowski, C. *Tetrahedron Lett.* **2001**, *42*, 8479-8481.
21. Characterization data for representative compounds: **1b** – white solid, mp = 243-245 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.67 (br s, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 8.10 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.24 (s, 1H), 7.16 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.3, 138.2, 135.6, 134.7, 131.6 (q, J_{C-F} = 50 Hz), 131.1, 131.0, 130.2 (unresolved q), 127.0, 125.2 (unresolved q), 123.0, 122.9, 120.8, 105.7. Anal. Calcd for $C_{16}H_{10}Br_3F_3N_2S$: C, 34.38; H, 1.80; N, 5.01. Found: C, 34.42; H, 1.88; N, 5.12. **1e** – beige solid, mp = 247-249 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.61 (br s, 2H), 8.28 (t, J = 1.5 Hz, 1H), 8.11 (d, J = 9.0 Hz, 2H), 8.07 (d, J = 7.5 Hz, 1H), 7.74 (m, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 9.0 Hz, 2H), 7.44 (s, 1H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 196.3, 169.2, 147.1, 138.0, 137.6, 134.2, 133.1, 132.4, 130.3, 130.2, 129.7, 128.2, 122.9, 107.5, 26.3; Anal. Calcd for $C_{17}H_{14}BrN_3O_3S$: C, 48.58; H, 3.36; N, 10.00. Found: C, 48.68; H, 3.42; N, 9.89. **1g** – off-white solid, mp = 239-

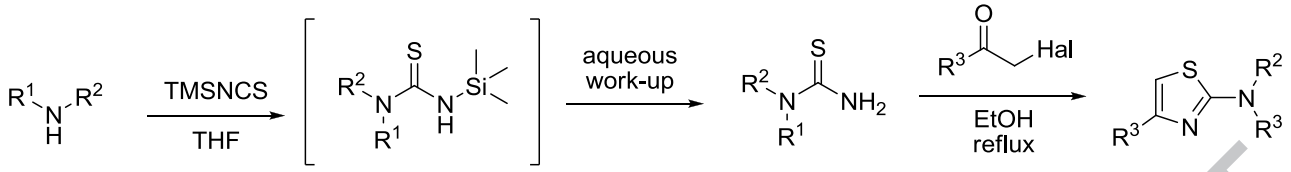
241 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (br s, 2H), 7.62 (dd, J = 8.0, 2.0 Hz, 1H), 7.59 (s, 1H), 7.31-7.33 (m, 3H), 7.29 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.24-7.26 (m, 2H), 2.28 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.5, 142.7, 133.4, 130.5, 129.8, 129.5, 129.3, 129.2, 127.9, 126.6, 121.0, 115.1, 19.8, 11.2; Anal. Calcd for $C_{17}H_{16}Br_2N_2S$: C, 46.38; H, 3.66; N, 6.36. Found: C, 46.51; H, 3.73; N, 6.29. **1v** – yellow oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (d, J = 8.0 Hz, 2H), 7.40 (t, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 1H), 6.70 (s, 1H). 3.57 (t, J = 7.0 Hz, 4H), 2.08 (quin, J = 7.0 Hz, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.4, 152.0, 128.4, 127.4, 126.1, 100.1, 49.5, 25.7; Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.88; H, 6.22; N, 12.08. **1w** – white solid, mp = 143-145 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.34 (s, 1H), 7.28-7.29 (m, 1H), 7.21-7.24 (m, 3H), 4.68 (s, 2H), 3.77 (t, J = 5.5 Hz, 2H), 2.97 (t, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.1, 148.9, 133.7, 133.4, 132.2, 130.9, 127.9, 127.2, 126.0, 125.9, 125.6, 119.9, 102.4, 48.8, 45.1, 27.2. Anal. Calcd for $C_{18}H_{15}BrN_2S$: C, 58.23; H, 4.07; N, 7.54. Found: C, 58.12; H, 3.96; N, 7.61.

22. Of the 23 compounds reported in this Letter, 19 had not been described in the literature, clearly attesting to the existing room for library expansion around the 2-aminothiazole chemotype. All of the compounds synthesized in this work have been deposited with the Queensland Compound Library (Griffith University) and are available for collaborative discovery projects.

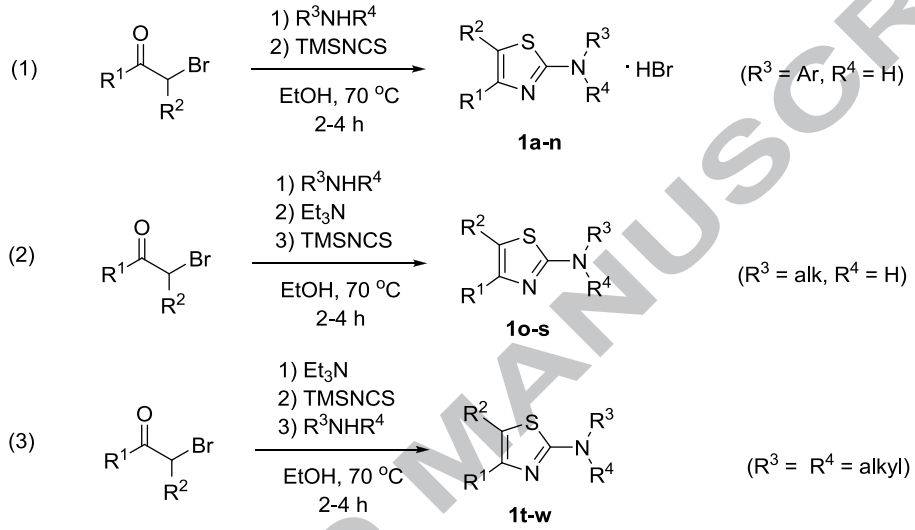
Scheme 1. Various isothiocyanate sources for 4-substituted 2-aminothiazole synthesis reported in the literature.



Scheme 2. Examples of the use of TMSNCS to prepare 2-aminothiazoles.[17]



Scheme 3. Multicomponent approach to 2-aminothiazoles developed in this work (see the general procedure for the order of addition of the reagents).



Scheme 4. A plausible mechanism for the multicomponent synthesis of 2-aminothiazoles.

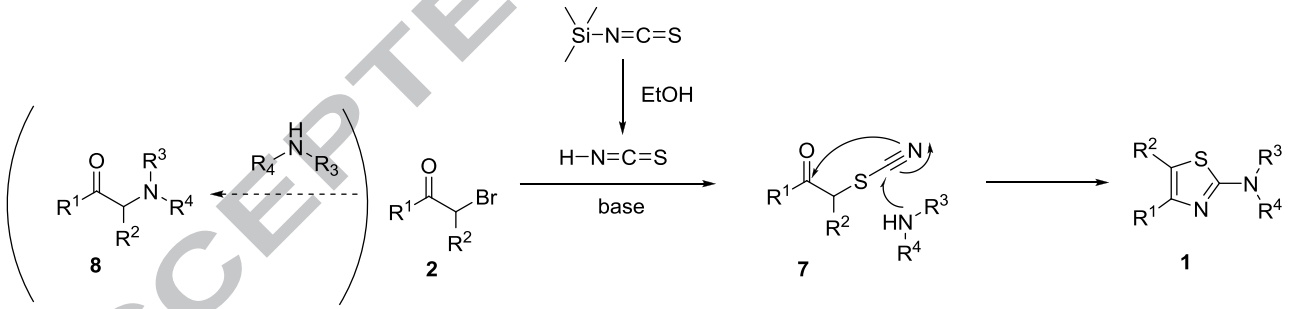
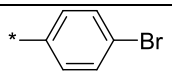
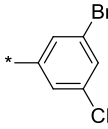
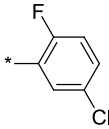
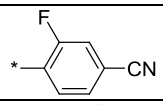
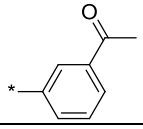
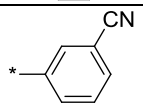
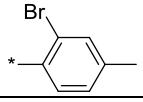
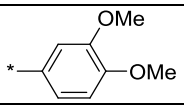
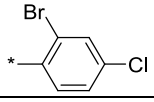
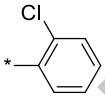
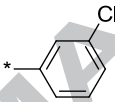
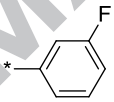
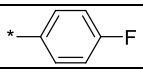
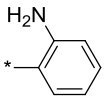
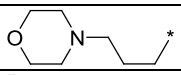
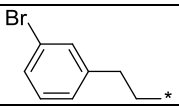
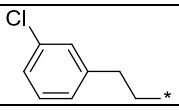
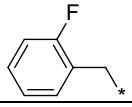
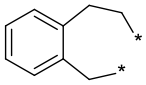


Table 1. 2-Aminothiazoles **1a-w** prepared in this work.

Entry	R^1	R^2	R^3	R^4	Yield (%) [a]
1a	Ph	H		H	92
1b	4-BrC_6H_4	H		H	78
1c	4-BrC_6H_4	H		H	69

1d	4-BrC_6H_4	H		H	73
1e	4-$O_2NC_6H_4$	H		H	66
1f	4-$O_2NC_6H_4$	H		H	70
1g	Ph	Me		H	95
1h	Ph	Me		H	93
1i	Ph	Me		H	82
1j	COOEt	H		H	66
1k	COOEt	H		H	83
1l	COOEt	H		H	77
1m	COOEt	H		H	78
1n	Ph	H		H	64
1o	Ph	H	Bn	H	58
1p	4-PhC_6H_4	H		H	67
1q	Ph	H		H	83
1r	4-BrC_6H_4	H		H	76
1s	4-BrC_6H_4	H		H	67
1t	Ph	H	-$CH_2CH_2OCH_2CH_2$-		83
1u	Ph	H	-$CH_2CH_2N(Et)CH_2CH_2$-		68
1v	Ph	H	-$CH_2CH_2CH_2CH_2$-		79
1w	4-BrC_6H_4	H			91

[a] Compounds **1a-n** were isolated as hydrobromide salts; compounds **1o-w** were isolated as free bases.