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A facile approach to the synthesis of 3,4-disubstituted-2-aminothiazolium derivatives through the use of a 'volatilizable' support

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ABSTRACT

A facile solid-phase synthetic approach to the synthesis of 3,4-disubstituted-2-aminothiazolium derivatives was reported. Functionalized aminomethylphenyl silica gel was used as a 'volatilizable' support. The products were cleaved with 10% HF and were obtained in high yields and purities.

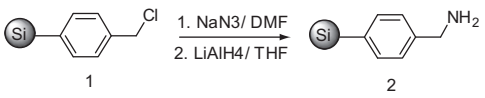
2-Aminothiazole is present in many chemically interesting compounds that display biological activity.[1] This ring structure can be either a substituent of a bioactive scaffold or the pharmacophore of bioactive molecules. Regarding 2-aminothiazole derivatives different activities have been reported for them such as antimicrobial, antibacterial, and anti-inflammation.[2] 2-Aminothiazole derivatives have also been tested as inhibitors of p53 to treat neurodegenerative disorders, as inhibitors of COX to treat pain, for the treatment of allergies, hypertension, Alzheimer's disease, and tumors.[3] 2-Aminothiazole was also reported to form a ruthenium (III) complex that exhibited promising antitumor properties.[4] Their wide range of biological activities has encouraged synthetic investigations toward facile strategies for the generation of large numbers of structurally diverse 2-aminothiazoles.

Solid-phase synthetic technology provides an ideal platform for the rapid assembly of building blocks to generate large collections of compounds having complex structures in a short time period.[5] Solid-phase synthesis, combined with high throughput screening is proven to be an efficient method for the discovery of lead compounds.[6] For the conventional solid-phase synthesis, all the desired synthetic products must be cleaved from the support and then separated from the spent support. This final separation step in the synthesis of very large numbers of compounds may result in reduced yields and in increased costs. To solve these problems, we first developed the concept of 'volatilizable' supports, which are completely decomposed and volatile following the cleavage step leaving only the desired product in the reaction vessel.[7] As part of this ongoing project, herein, we provide a facile approach to the synthesis of 3,4-disubstituted-2-aminothiazolium derivatives by the use of a 'volatilizable' support.

The functionalized aminomethylphenyl silica gel was used as the 'volatilizable' support. The aminomethylphenyl-functionalized silica gel was synthesized by the on-resin substitution and reduction of chloromethylphenyl-functionalized silica gel **1**[8] as shown in Scheme 1. The chloromethylphenyl-functionalized silica gel **1** (loading: 0.35 mmol/g) was treated with sodium azide in DMF at 65 °C for 24 h. After washing with DMF, the functionalized silica gel was then reduced with 0.1 M lithium aluminum hydride at room temperature overnight to yield the desired aminomethylphenyl-functionalized silica gel **2**. The loading of the resin was 0.3 mmol/g, which was determined from the substitution of the Fmoc-Ala-loaded resin by coupling Fmoc-Ala-OH and then cleaving with 10% HF.

The 3,4-disubstituted-2-aminothiazolium derivatives were synthesized by on-resin cyclization of resin-bound thiourea derivatives with α-halogenoketones (Scheme 2).[9] Starting from aminomethylphenyl-functionalized silica gel **2**, a Boc-amino acid was coupled on the resin to generate the resin-bound amino acid **3**. After removal of the Boc group, an isothiocyanate was coupled to yield the resin-bound thiourea **4**. The resin-bound thiourea **4** was then reacted with an α-bromoketone, resulting in the resin-bound 2-iminothiazole **5**. After treatment of 10% HF at room temperate for 1 h, followed by the removal of the solvent under vacuum, the final product of 3,4-disubstituted-2-aminothiazolium **6** was obtained in high yield and purity (Table 1, 6a–k). The product was generated with the R^1 position functionality protected by using side-chain protected amino acids; for example, Boc-Ser(Bzl)-OH and Boc-Lys(2-Cl-Z)-OH (6j–k).

To obtain an unprotected side-chain group at the R^1 position, Fmoc-amino acids such as Fmoc-Ser(*t*Bu)-OH, Fmoc-Thr(*t*Bu)-OH, and Fmoc-Tyr(*t*Bu)-OH were used instead of Boc-amino acid. After removal of the Fmoc protecting group with 20% piperidine, isothiocyanates and α-bromoketones were coupled step-wise using the same reaction conditions as shown in Scheme 1 to yield the



Scheme 1. Synthesis of functionalized aminomethylphenyl silica gel.

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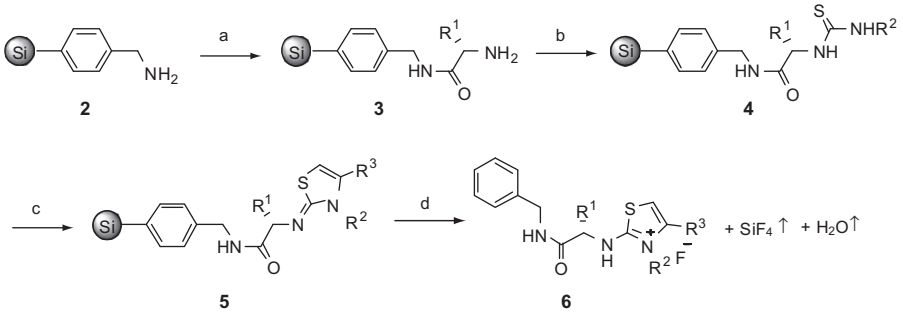

Scheme 2. Synthesis of 2-aminothiazol-3-ium derivatives through a 'volatilizable' amino-functionalized silica gel. Reagents and conditions: (a) Boc-AA-OH/DIC; 55% TFA/DCM; (b) R^2NCS/DCM; (c) α-bromoketone, 65 °C, overnight; (d) 10% HF, rt, 1 h.

Table 1
Individual products of 3,4-disubstituted-2-aminothiazolium derivatives

Entry	R^1	R^2	R^3	Purity%[a]	Yield%[b]
6a	$-CH_3$	$-C_6H_5$	$-C_2H_5$	92	84
6b	$-CH_3$	$-C_6H_4(p\text{-}OCH_3)$	$-C(CH_3)_3$	91	88
6c	$-CH_2C_6H_5$	$-C_6H_5$	$-C_2H_5$	90	99
6d	$-CH_2CH(CH_3)_2$	$-C_6H_4(p\text{-}CH_3)$	$-C_6H_5$	90	86
6e	$-CH_2CH(CH_3)_2$	$-C_6H_4(o\text{-F})$	$-C_6H_4(p\text{-F})$	80	80
6f	$-CH(CH_3)_2$	$-C_6H_4(p\text{-}NO_2)$	$-C_2H_5$	86	96
6g	$-CH(CH_3)_2$	$-C_6H_4(o\text{-Cl})$	$-C_6H_5$	90	99
6h	–H	$-C_6H_3(o,o\text{-}2CH_3)$	$-C(CH_3)_3$	90	93
6i	–H	$-C_6H_3(o,p\text{-}2Cl)$	$-C(CH_3)_3$	85	80
6j	$-CH_2O-Bzl$	$-C_6H_4(p\text{-}NO_2)$	$-C_2H_5$	70	73
6k	$-(CH_2)_4NHCOOCH_2C_6H_4(o\text{-Cl})$	$-C_6H_4(p\text{-}CH_3)$	$-C_6H_5$	78	74
6l	$-CH_2OH$	$-C_6H_4(p\text{-}OCH_3)$	$-C_6H_5$	85	90
6m	$-CHCH_3OH$	$-C_6H_4(p\text{-}OCH_3)$	$-C_6H_5$	78	82
6n	$-C_6H_4OH$	$-C_6H_4(p\text{-}OCH_3)$	$-C_6H_5$	81	84

[a] Purity (in %) is determinate by the peak area of HPLC at 214 nm.
[b] Yields (in %) are based on the weight of crude product and are relative to the substitution of the resin.

resin-bound 2-iminothiazole **5**. The resin- bound 2-iminothiazole **5** was then treated with a solution of TFA/water/triisopropylsilane (95:2.5:2.5 by volume) for 1.5 h at room temperature to remove the amino acid side-chain protecting groups. After treatment of 10% HF the final products of 3,4-disubstituted-2-aminothiazolium derivatives with unprotected side-chain groups at the R^1 position were obtained (Table 1, 6l–n).

In summary, we present herein, a straightforward approach to the synthesis of 3,4-disubstituted-2-aminothiazolium derivatives through the use of 'volatilizable' aminomethylphenyl-functionalized silica gel. Boc- and Fmoc-amino acids were both used in the synthetic process, resulting in the protected-and unprotected-products at R^1 position, respectively. The use of 10% HF in water for the cleavage of the products not only avoids the use of harsh cleavage conditions such as anhydrous HF, but also provides a facile method for isolating the desired products through the decomposition of the silica-based support. The use of functionalized-aminomethylphenyl silica gel to make heterocyclic compounds is efficient and promising.

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9. General procedure for the synthesis of the 3,4-disubstituted-2-aminothiazolium derivatives: 200 mg functionalized aminomethylphenyl silica gel was sealed within a polypropylene mesh packet.[5b] Reactions were carried out in

polypropylene bottles. A solution of *N*-Boc-amino acid (5 equiv, 0.1 M in DMF), HOBt (5 equiv, 0.1 M in DMF), and DIC (5 equiv, 0.1 M in DMF) were added to the reaction vessel. The reaction was shaken at room temperature for 2 h, followed by washing with DMF (three times). Upon removal of the Boc- group with 55% TFA in DCM at room temperature for 30 min, the resin was washed and neutralized with 5% DIEA in DCM. The resin-bound amine was reacted with isothiocyanate (5 equiv, 0.1 M in DCM) overnight. After washing with DCM (two times), DMF (one time),and DCM (two times) and air dried, α-bromoketone (10 equiv, 0.1 M in DMF) was added to the reaction vessel. The reaction was performed at 65 °C for 24 h. The resin packet was then washed with DMF (three times), DCM (three times) and MeOH (three times). The cleavage of the product was carried out by the treatment with 4 ml of 10% HF at room temperature for 1 h, followed by lyophilization to remove the solvent. The product of 2-aminothiazol-3-ium derivatives was obtained. The representative product **6d** was characterized by electrospray LC–MS under ESI conditions and NMR. HPLC: t_R = 2.8 min, CH_3CN(+ 0.05% formic acid) in H_2O (+ 0.05% formic acid), 5–95% in 6 min; column: luna C_{18}, 5 μm, 50 × 4.60 mm, detection 254 nm; ESI-MS (*m*/*z*) of **6d**: 469.2 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ: 0.84 (d, 6H, *J* = 6.5 Hz), 1.41–1.44 (m, 1H), 1.54–1.61 (m, 2H), 2.22 (s, 3H), 3.42–3.44 (m, 1H), 4.25 (d, 2H, *J* = 6.5 Hz), 6.44 (s, 1H), 6.54 (s, 1H), 7.04 (m, 4H), 7.12–7.17 (m, 4H), 7.20–7.26 (m, 4H), 7.30–7.33 (m, 2H), 7.48 (t, 1H, *J* = 5.5 Hz); C NMR (125 MHz, DMSO-d_6) δ: 22.0, 22.8, 24.5, 40.0, 41.9, 66.7, 97.0, 126.7, 127.0, 128.0, 128.2, 128.3, 128.6, 129.2, 131.3, 135.6, 136.6, 139.2, 139.4, 159.9, 172.3.