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A simple solid-phase synthesis of disubstituted guanidines using Rink amide resin as an amine component

Min Li,* Lawrence J. Wilson and David E. Portlock

Procter & Gamble Pharmaceuticals, Health Care Research Center, 8700 Mason-Montgomery Road, Mason, OH 45040, USA

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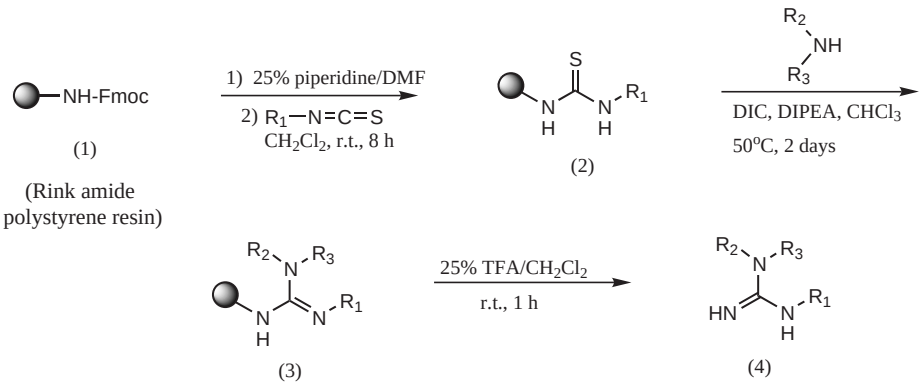
Abstract—A practical solid-phase synthesis that simply uses Rink amide resin as an amine component in reacting with aromatic isothiocyanates and aliphatic amines to generate disubstituted guanidines is described. No special linker or guanylation reagents are involved in this method. The product is obtained in a 'traceless-linker' fashion and in high yield and purity when an electron-deficient isothiocyanate is employed.

Substituted guanidines are well known to be important pharmacophores in many therapeutic areas, e.g. anti-hypertensive, cardiotonic, H_2 antagonist/agonist and anti-tumor activity.[1] Interest in making substituted guanidines on solid support has been rapidly growing in recent years.[2] Many of the known methods either involve special linkers and reagents,[3] or leave the generated guanidine with a linker trace, usually as an acid or amide.[4] As an on-going effort in the solid-phase synthesis of small drug-like organic molecules,[5] we earlier reported a traceless-linker approach to substituted guanidines by utilizing a novel acyl isothiocyanate linker.[6] Herein, we wish to report a simple, clean, high yielding and linker-free method for the synthesis of disubstituted guanidines by using Rink amide resin as an amine component.

During a study of the solid-phase synthesis of substituted guanidines and guanidine derivatives,[7] we found that Rink amide resin can be simply used as an amine component in reactions with isothiocyanates and amines to generate disubstituted guanidines in a traceless-linker fashion. The general procedure (Scheme 1) includes two major steps: isothiocyanate addition and guanylation. The commercial Rink amide resin (**1**) was deprotected with 25% piperidine/DMF, and then treated with an isothiocyanate (5 equiv.) in CH_2Cl_2 to give the resin bound thiourea (**2**). The thiourea **2** was subjected to guanylation with an amine (5 equiv.) at 50°C in $CHCl_3$ in the presence of DIC (5 equiv.) and DIPEA (5 equiv.) to give the resin bound guanidine (**3**). The disubstituted guanidine (**4**) was then cleaved under mild Rink resin cleavage conditions (25% TFA/CH_2Cl_2 at room temperature).



Scheme 1. Solid-phase synthesis of disubstituted guanidines using Rink amide resin.

Keywords: disubstituted guanidines; solid-phase synthesis; Rink amide resin.

* Corresponding author. E-mail: lim2@pg.com; lwilson3@prius.jnj.com; portlockde@pg.com

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The addition of the amino group from Rink resin to an isothiocyanate is very efficient for both aromatic and aliphatic isothiocyanates. However, the structural effect becomes more significant in the guanylation step. Similar to what was found previously, under these guanylation conditions, aromatic isothiocyanates and aliphatic amines are the most suitable substrates.[7] The thiourea formed from an aromatic isothiocyanate with an electron-withdrawing group is more favorable to the guanylation. It is also understandable that with this particular amine component from the Rink amide linker, the guanylation could be more difficult for those thioureas formed from less electrophilic isothiocyanates. Therefore, unreacted thiourea intermediate was the primary by-product in these cases. Typical yields and purities for disubstituted guanidines made via this method by utilizing the Argonaut Quest 210 are listed in Table 1. With suitable substrates, especially aromatic isothiocyanate with an electron-withdrawing group, the synthesis is very efficient in providing high yield and purity for disubstituted guanidines.

In conclusion, we have developed a simple and convenient solid-phase synthetic method to prepare disubstituted guanidines. No special linker or reagents are involved in this method. By utilizing Rink amide resin as an amine input and following a short two-step synthesis, isothiocyanate addition and guanylation, the method generates disubstituted guanidines in good yield and purity from aromatic isothiocyanates and aliphatic amines. It is important to note that aliphatic isothiocyanates and anilines did not work well under this particular synthetic system. With this limitation in mind, the method is suitable for the combinatorial synthesis of compounds of this type.

Acknowledgements

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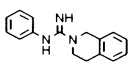
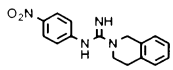
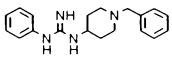
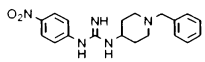
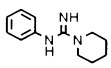
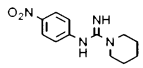
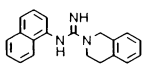
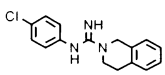
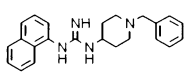
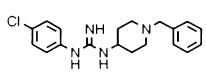
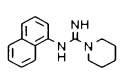
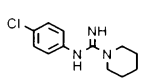
Table 1. Typical yields and purities of disubstituted guanidines synthesized by this method[8]

	Product	Overall Yield (%)[a]	Purity (%)[b]		Product	Overall Yield (%)[a]	Purity (%)[b]
4a		71	70	4g		87	90
4b		77	54	4h		95	85
4c		70	56	4i		96	95
4d		95	86	4j		100	83
4e		98	91	4k		99	83
4f		89	75	4l		88	83

a) Crude 4-step overall yields as a mono-TFA salt. Determined by weight based on the loading of the commercial Rink amide resin. b) Determined by HPLC at 210 nm.

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8. General procedure for the synthesis of disubstituted guanidines on the Argonaut Quest 210 (each step was repeated once except the cleavage step): The commercial Rink amide polystyrene resin (0.3 g; 0.7 mmol/g; Advanced ChemTech) was treated with 25% piperidine/DMF (4 ml) at room temperature for 1 h, filtered and washed successively with DMF (three times), CH_2Cl_2 (three times), MeOH (three times) and CH_2Cl_2 (three times). To a slurry of the deprotected resin in CH_2Cl_2 (4 ml) was added isothiocyanate (5 equiv.), and the mixture was agitated at room temperature for 8 h. The resin was filtered and washed in the same way as above. The resin was then treated with amine (5 equiv.), DIC (5 equiv.) and DIPEA (5 equiv.) in $CHCl_3$ (4 ml) at 50°C for 2 days, filtered, washed in the same way as above. The resin was cleaved with 25% TFA/CH_2Cl_2 (4 ml) at room temperature for 1 h, filtered, and washed with CH_2Cl_2 and MeOH. The filtrate was evaporated to dryness by SpeedVac (Savant Instruments, Inc.) to give the desired product in yield and purity, as shown in Table 1. Analytical data for representative compounds:

4f: ^{1}H NMR (300 MHz, CD_3OD) δ 8.09–7.52 (m, 7H), 3.75 (m, 4H), 1.88 (bs, 6H); ^{13}C NMR (300 MHz, CD_3OD) δ 157.8, 136.7, 133.3, 131.5, 130.4, 130.2, 128.8, 128.3, 127.4, 126.7, 123.4, 49.3, 27.0, 25.3; HRMS (FAB) m/z for $C_{16}H_{19}N_3$ $(M+Na)^+$ calcd: 276.1476, found: 276.1467.

4g: ^{1}H NMR (300 MHz, CD_3OD) δ 8.25 (d, 2H, $J=9.0$ Hz), 7.43 (d, 2H, $J=9.0$ Hz), 7.21 (m, 4H), 4.72 (s, 2H), 3.77 (t, 2H, $J=6.0$ Hz), 3.03 (t, 2H, $J=6.0$ Hz); ^{13}C NMR (300 MHz, CD_3OD) δ 156.8, 146.6, 145.1, 136.1, 132.8, 129.7, 129.2, 128.5, 127.8, 126.8, 124.2, 49.7, 46.7, 29.7; HRMS (FAB) m/z for $C_{16}H_{16}N_4O_2$ $(M+H)^+$ calcd: 297.1352, found: 297.1359.

4k: ^{1}H NMR (300 MHz, CD_3OD) δ 7.58–7.29 (m, 9H), 4.40 (s, 2H), 3.86 (m, 1H), 3.62 (m, 2H), 3.14 (m, 2H), 2.29 (m, 2H), 1.95 (m, 2H); ^{13}C NMR (300 MHz, CD_3OD) δ 156.7, 135.6, 134.5, 132.8, 131.8, 131.5, 130.8, 130.6, 128.3, 62.0, 52.7, 37.4, 30.6; HRMS (FAB) m/z for $C_{19}H_{23}ClN_4$ $(M+H)^+$ calcd: 343.1690, found: 343.1679.