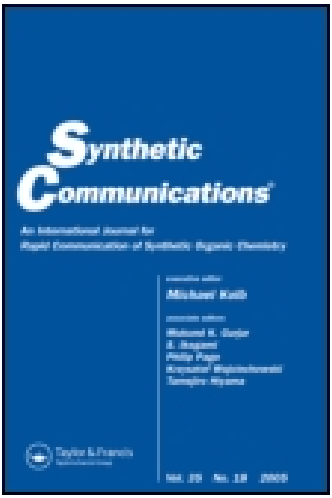

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Solid-Phase Synthesis of N-Aryl-N′-Carboalkoxy Guanidines by the Mitsunobu Reaction of Fmoc-Guanidines

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Published online: 30 Mar 2009.

To cite this article: Dale E. Robinson , Punit P. Seth & Elizabeth A. Jefferson (2004) Solid-Phase Synthesis of N-Aryl-N′-Carboalkoxy Guanidines by the Mitsunobu Reaction of Fmoc-Guanidines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:15, 2743-2749, DOI: 10.1081/SCC-200026206

To link to this article: http://dx.doi.org/10.1081/SCC-200026206

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 15, pp. 2743–2749, 2004

Solid-Phase Synthesis of *N*-Aryl-*N*′-Carboalkoxy Guanidines by the Mitsunobu Reaction of Fmoc-Guanidines

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ABSTRACT

A new method for the solid-phase synthesis of *N*-aryl-*N*′-carboalkoxy guanidines is described. Aromatic amines were reacted with Fmoc-isothiocyanate to provide Fmoc-thioureas, which were coupled with Rink amide resin to provide the corresponding resin-bound Fmoc-guanidines. Subsequent Mitsunobu alkylation with a variety of alcohols delivered *N*-aryl-*N*′ carboalkoxy guanidines in good to high purity after resin cleavage.

Key Words: Carbamoylguanidines; Mitsunobu reactions; Rink amide resin; Fmoc-isothiocyanate.

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DOI: 10.1081/SCC-200026206 0039-7911 (Print); 1532-2432 (Online)

INTRODUCTION

The importance of the guanidine functionality as a biologically relevant pharmacophore is well documented.[1,2] For applications in our small molecule RNA targeting anti-bacterial and anti-viral programs,[3] we needed access to a diverse set of *N*-aryl-*N*′-carboalkoxy guanidines such as compound **5**. While the preparation of carboalkoxy substituted guanidines has been described in the literature, these methods have been limited to using the carboalkoxy substituent as a protecting/activating group which is typically removed at the end of the synthesis.[4–7] In our case, however, we wished to retain the carboalkoxy substituent on the guanidine and also use it as a site to incorporate diversity. A review of the existing methods[8–11] indicated no suitable procedure that would allow for the solid-phase synthesis of a diverse set of carboalkoxy guanidines. As a result we decided to investigate alternate strategies to prepare these guanidine derivatives on solid support.

Recently, Zaragoza[12] reported the preparation of *O*-carbamates on solid phase by reacting support-bound Fmoc-amines with alcohols under Mitsunobu conditions. We rationalized that a similar strategy using support-bound Fmoc-guanidines instead of Fmoc-amines should provide access to carboalkoxy guanidines. To examine the feasibility of this strategy, the synthetic plan outlined in Sch. 1 was proposed. Reaction of Rink amide resin[13][a] and Fmoc-thiourea **2** in the presence of a suitable activating agent should provide Fmoc-guanidine **3**. Subsequent alkylation with alcohols under Mitsunobu conditions should provide the desired *N*-aryl-*N*′-carboalkoxy guanidine **5**. Such a strategy would enable us to prepare the desired carboalkoxy guanidines in a traceless manner and also allow for concurrent introduction of diversity on the aromatic ring and the carboalkoxy substituent (Sch. 1).

A set of aromatic amines $ArNH_2$ (**A**–**H**), were reacted with Fmoc-isothiocyanate in CH_2Cl_2 to provide the corresponding Fmoc-thioureas **2** (Sch. 2). Rink amide resin was deprotected with piperidine and treated with excess Fmoc-thioureas **2** and diisopropylcarbodiimide (DIC). We were pleased to find that in all cases, arylguanidines **6** were isolated in high yield (89–95%) and purity (>90%) after Fmoc deprotection and resin cleavage.[b]

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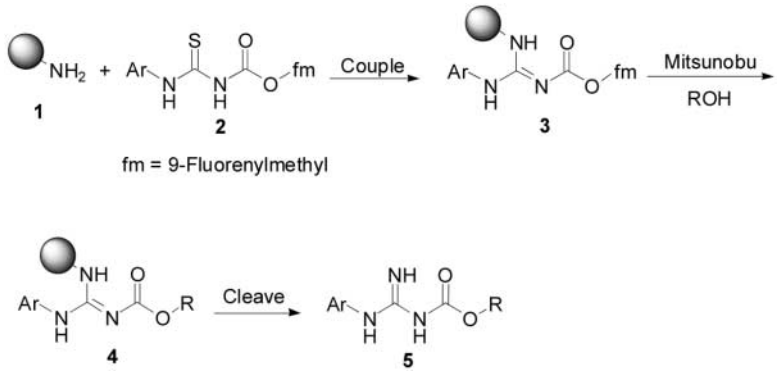
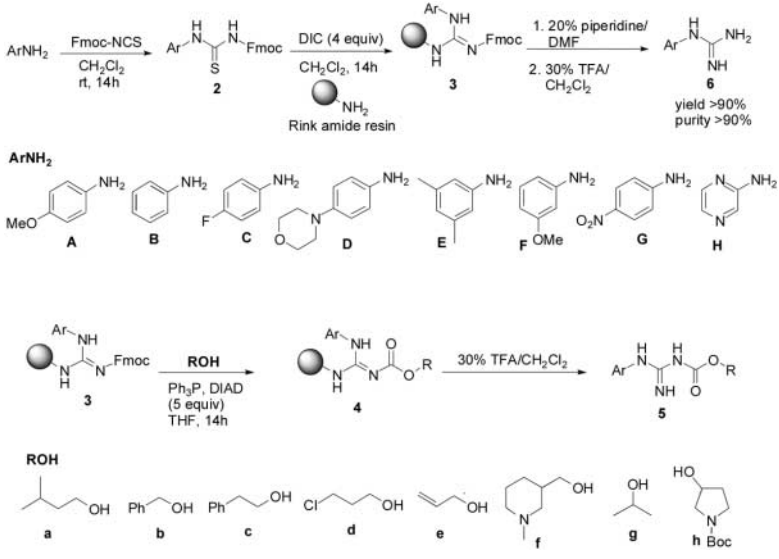
[a]In this report Rink amide resin was reacted with arylisothiocyanates to provide resin-bound arylthioureas. Further coupling with primary amines in the presence of DIC provided disubstituted guanidines after resin cleavage.

[b]The resin-bound guanidines obtained after deprotection of the Fmoc group in **3** (but prior to acid cleavage) were sufficiently nucleophilic to react with other electrophiles such as sulfonyl and acyl chlorides. We are currently investigating these reactions to further expand the scope of this method to prepare sulfonyl- and acyl-guanidine derivatives.



Scheme 1. Solid-phase synthesis of *N*-aryl-*N*′-carboalkoxy guanidines.

If resin-bound Fmoc-guanidines **3** were not treated with piperidine/DMF prior to acid cleavage, then the corresponding Fmoc-guanidines were isolated as the major products. Best results for the couplings were obtained when DIC was used as the activating agent, although, EDC (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) could also be used. Lower yield and purities were observed when Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) was used as the coupling reagent.[8]



Scheme 2. Preparation of *N*-aryl-*N*′-carboalkoxy guanidines.

The above outcome was significant as it demonstrated the ability of the amine functionality on the resin to essentially scavenge the activated Fmoc-thioureas from the reaction mixture and create a guanidine linkage directly on the resin. These results were also gratifying as they allayed our earlier concerns that the Fmoc protecting group on the thiourea may be too labile to undergo efficient coupling with the amine resin.

We next examined the utility of support-bound guanidines **3** to prepare the requisite *N*-aryl-*N*′-carboalkoxy guanidines. Resin-bound arylguanidines **3** were reacted with alcohols ROH (**a**–**h**) under Mitsunobu conditions (Sch. 2). Analysis of the cleaved products indicated clean formation of carboalkoxy guanidines **5** (Table 1). In general, primary aliphatic alcohols provided the best results (entries 1–5) although a primary alcohol containing a basic amine functionality provided no desired product (entry 6). Secondary alcohols provided carboalkoxy guanidines in lower yield and purity (entries 7–8). In almost all cases, the major byproduct was identified to be the

Table 1. Representative *N*-aryl-*N*′-carboalkoxy guanidines prepared by solid-phase synthesis.

Entry	ROH	$ArNH_2$	5[a] (mass)	5[b] $[M+H]^+$	Purity[c] (%)	Yield[d] (%)
1	**a**	**A**	279.16	280.2	95	91
2	**b**	**A**	299.13	300.2	95	89
3	**c**	**A**	313.14	314.2	95	85
4	**d**	**A**	285.09	286.1	85	90
5	**e**	**A**	249.11	250.2	70	77
6	**f**	**A**	320.18	—	0	0
7	**g**	**A**	251.13	252.2	71	72
8	**h**	**A**	278.14	279.2	50[e]	69
9	**a**	**B**	249.15	250.2	95	86
10	**a**	**C**	267.14	268.2	95	78
11	**a**	**D**	334.20	335.3	80	75
12	**a**	**E**	277.18	278.2	70	87
13	**a**	**F**	279.16	280.3	95	86
14	**a**	**G**	294.13	—	0	0
15	**a**	**H**	251.14	252.2	86	91

[a]Calculated exact mass.
[b]Observed m/z.
[c]Purity determined using an evaporative light scattering detector (ELSD).
[d]Percent yield determined by crude mass recovery based on initial loading of Rink-NH_2.
[e]Product was contaminated with Ph_3PO.

corresponding deprotected guanidine **6** (5–20%). A number of different Fmoc-guanidines derived from substituted anilines were found to participate in the reaction (entries 9–13). Use of 4-nitroaniline provided no desired carbamoylguanidine, presumably due to difficulty in forming the Fmoc-thiourea during reaction with Fmoc-isothiocyanate (entry 14). An Fmoc-guanidine derived from a heterocyclic amine was also found to participate in the reaction and provide the corresponding carboalkoxy guanidine (entry 15).

In order to expand the scope of the method, the Mitsunobu reaction of a support-bound Fmoc-guanidine derived from an aliphatic amine was also attempted. To this end, resin-bound *N*-Fmoc-*N′*-phenethylguanidine was prepared and reacted with 4-methylbutanol.[c] Once again, the major product after acid cleavage was identified to be that arising from O-alkylation of the carbamoyl group (50%), while the major contaminant appeared to be unreacted *N*-Fmoc-*N′*-phenethylguanidine (45%). From this result, it appears that under the conditions employed, guanidines derived from aromatic amines are more reactive that guanidines derived from aliphatic amines.

To our knowledge, this is the first report that describes the O-alkylation of Fmoc-guanidines with alcohols under Mitsunobu conditions. No products arising from N-alkylation of the carbamate nitrogen were detected during LC–MS analysis of the cleavage products. This is in direct contrast to the results obtained during Mitsunobu alkylation of *N*-Boc guanidines, where the major product arises from alkylation of the carbamate nitrogen.[14,15] It also appears that the O-alkylation under Mitsunobu conditions is limited to Fmoc-guanidines as guanidines prepared from aromatic amines using ethoxycarbonylisothiocyanate or benzoylisothiocyanate were found not to participate in the reaction. In these cases, only the corresponding ethoxycarbonyl or benzoyl guanidines were isolated after acid cleavage. The above results suggest that cleavage of the fluorenyl group occurs first to generate resin-bound guanidine-carbamates, which then undergo further reaction with activated alcohols to provide the O-alkylated products.[7]

In summary, we have described a new strategy for the preparation of *N*-aryl-*N′*-carboalkoxy guanidines. Using this method, a diverse set of carboalkoxy guanidines were prepared from aromatic, heteroaromatic and aliphatic amines, and Fmoc-isothiocyanate. The synthesis also highlights a new O-alkylation reaction of resin-bound Fmoc-guanidines under Mitsunobu conditions.

[c]A mixture of *N*-Fmoc-*N′*-phenethylthiourea (4 eq.), EDC (4 eq.), DIPEA (8 eq.) in CH_2Cl_2 was reacted with Rink-NH_2 using the general procedure described to prepare the resin bound *N*-Fmoc-*N′*-phenethylguanidine. In this case very poor results were obtained when DIC was used as the coupling agent.

EXPERIMENTAL

General Procedure for the Synthesis of *N*-aryl-*N*′-Carboalkoxy Guanidines on the Argonaut Quest 210

Argogel®-Rink-NH-Fmoc resin (0.32 mmol/g, 150 mg, 0.048 mmol) was deprotected with 25% piperidine/DMF (2.5 mL) at rt for 2 hr, filtered and washed with DMF (3X), CH_2Cl_2 (2X), MeOH (2X), and CH_2Cl_2 (3X). A solution of Fmoc-arylthiourea **2** (0.2 mmol, prepared in situ by reacting 0.2 mmol of arylamine with 0.2 mmol of Fmoc-isothiocyanate in 2.5 mL of CH_2Cl_2 at rt for 14 hr) was added to the resin and the mixture was agitated at rt for 14 hr, filtered and washed with CH_2Cl_2 (2X), MeOH (2X), CH_2Cl_2 (3X), and dry THF (2X). A solution of the desired alcohol ROH (0.24 mmol), DIAD (2.4 mmol, 0.048 mL) and triphenylphosphine (0.24 mmol, 0.063 g) in dry THF (2.5 mL) was added to the resin and the mixture was agitated at rt for 14 hr, filtered and washed with CH_2Cl_2 (3X), MeOH (3X), and CH_2Cl_2 (3X). The resin was cleaved with 25% TFA/CH_2Cl_2 (3 mL) at rt for 90 min, filtered and washed with CH_2Cl_2. The combined filtrate was evaporated to dryness by SpeedVac (Savant Instruments, Inc.) to provide the desired product in yield and purity as shown in Table 1.

Analytical Data for Representative Guanidines

5Aa. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33 (2H, d, $J = 9.0$), 7.10 (2H, d, $J = 9.0$), 4.38 (2H, t, $J = 6.7$), 3.88 (3H, s), 1.79 (1H, m), 1.66 (m, 2H), 1.01 (6H, d, $J = 6.5$).

5Ba: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (5H, m), 4.36 (t, 2H, $J = 6.7$), 1.79 (1H, m), 1.66 (m, 2H), 0.99 (6H, d, $J = 6.5$).

5Ha: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.34 (m, 2H), 4.28 (t, 2H, $J = 6.8$), 1.70 (1H, m), 1.58 (m, 2H), 0.99 (6H, d, $J = 6.5$).

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Received in the USA March 31, 2004