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Preparation of *N*-alkyl-*N*′-carboalkoxy guanidines: unexpected effective trans-alkoxylation transforming the 2,2,2-trichloroethoxycarbonyl into various carbamates

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Abstract—A range of *N*-alkyl-*N*′-Boc guanidines was simply synthezized from monoprotected Boc-1*H*-pyrazole-1-carboxamidine by reaction with primary amines. Synthesis of the hindered (*R*)-*N*-methylbenzyl-*N*′-Troc guanidine was achieved from the corresponding thiourea by the action of ammonia. Transformation of the Troc group into others carbamate groups, including Boc, was simply obtained by refluxing in the appropriate alcohol.
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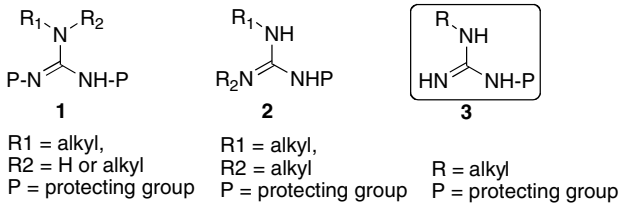
The guanidine group has attracted considerable attention recently, since it is found in a wide array of biologically active compounds.[1] Guanidine-containing compounds have been isolated from natural sources such as algae, sponges, and micro-organisms.[2] The importance of the guanidine functional group has stimulated important synthetic research. This has led to a number of methods of preparation of N,N′-disubstituted and N,N′-diprotected guanidine species of type **1**–**3** using solution-phase as well as solid-phase synthesis (Scheme 1).[3]

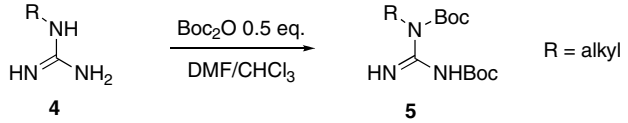
As far as we are concerned we sought to prepare a large library of *N*-alkyl-*N*′-carboalkoxy guanidines of type **3**.



Scheme 1.

A number of syntheses of *N*-alkyl-*N*′-protected guanidines have been reported,[4] but there was no report of a general method for the synthesis of *N*-alkyl-*N*′-carboalkoxy guanidines. One example dealt with the carbamoylation of *N-iso*propylguanidine by treatment with a di-*tert*-butyldicarbonate (Boc_2O) or di-benzyldicarbonate.[5] Unfortunately, this method was not suitable for a general application; when we ran the reactions on our N-alkylated guanidines, we systematically ended up with *N*-alkyl-*N*,*N*′-bis protected guanidines **5** as major compounds even when 0.5 equiv of Boc_2O was used (Scheme 2).

To circumvent this result, we envisioned then to prepare the orthogonally protected 1*H*-pyrazole-1-carboxamidine **7** and to displace the pyrazole leaving group by primary amines to give **8**.[6,7] Further selective monodeprotection would afford guanidines **9a**–**k** (Scheme 3). We choose this two step route owing to the literature reporting that the reactivity of the N-monoacylated 1*H*-pyrazol-1-carboxamidine **10** toward primary amines was dramatically reduced.[6]



Scheme 2.

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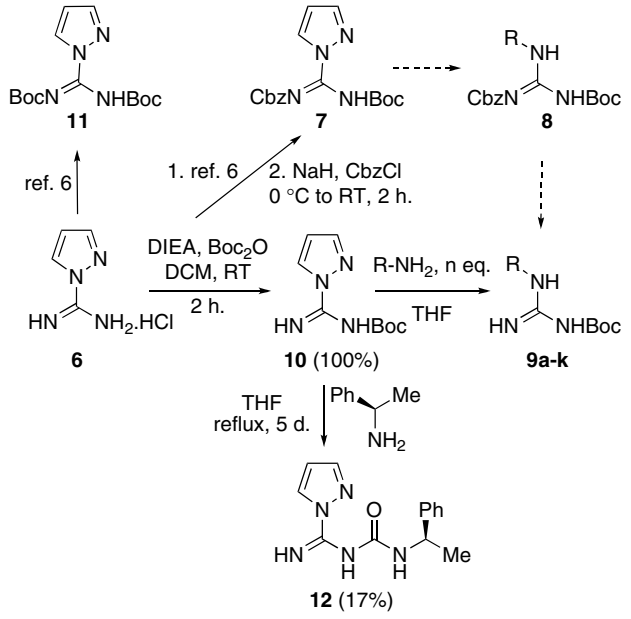
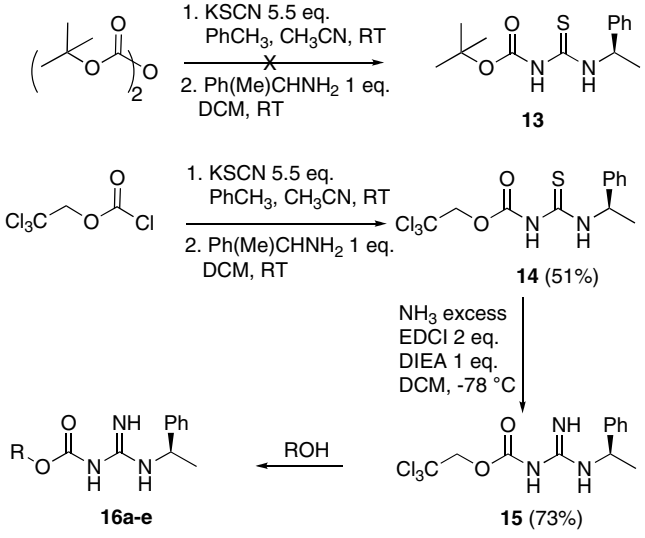


Scheme 3.

Unfortunately, the required diprotected pyrazole **7**, prepared from the commercially available **6**, was unstable during the purification step and could not be used to test its reactivity toward amines. This result hampered the preparation of the guanidines of type **8** and further deprotection into the desired derivatives of type **9**. Surprisingly, the reported di-Boc **11**[6] that we prepared is much more stable than **7** under the same conditions. We suspect that the different withdrawing electron effects of Cbz and Boc groups cause an electronic imbalance rendering **7** very unstable. ^{1}H NMR shifts of **7** and **11** are indeed very different.[8] This result prompted us to study the direct amination of the monoprotected Boc **10**. To our surprise, and in contrast to the literature,[6] *N*-Boc-1*H*-pyrazole-1-carboxamidine (**10**) and primary amines underwent substitution reactions giving the desired *N*-alkyl-*N*′-Boc guanidines **9a**–**f** and **9h**–**k** in good to excellent yields (Table 1).

Unhindered primary amines underwent substitution reactions to give guanidines **9a**–**d** in good to excellent yields (entries 1–4). More bulky amines gave **9e**–**f** in good yields when refluxed for longer reaction times (entries 5–6). In the case of the (*R*)-methylbenzylamine (entry 7), the substitution reaction did not proceed on the amidine carbon, but on the carbonyl function of the Boc group to give **12** in 17% yield, together with unreacted starting material **10**. Aniline and derivatives gave **9h**–**k** in moderate yields (entries 8–11). Longer reaction times caused the progressive degradation of the products.

As the above method does not entirely solve the problem of a general preparation of a large guanidine library including hindered primary amines, we explored an alternative pathway building substituted guanidines from carbamoyl isothiocyanate via thiourea derivatives.[9] Direct preparation of the Boc derivative **13** from potassium thiocyanate and Boc_2O failed (Scheme 4). The feasibility of this approach was tested with the 2,2,2-trichloroethoxycarbonyl (Troc) group as protecting group. To avoid the problem of steric hindrance during the nucleophilic attack of the second amine on the thiourea intermediate, we planned to first add (*R*)-methylbenzylamine, and then to introduce the not protected nitrogen by unprecedented direct reaction with ammonia in the presence of the coupling reagent (Scheme 4).[10] Reaction of potassium thiocyanate with trichloroethylchloroformate gave the intense yellow Troc isothio-



Scheme 4.

Table 1. *N*-Alkyl-*N*′-Boc guanidines **9** produced via Scheme 3

Entry	R (*n* equiv)	Reaction conditions			Product (yield %)[b]
1	Methyl (1.5 equiv)		rt	5 h	**9a** (95)
2	*n*-Propyl (2 equiv)		rt	16 h	**9b** (93)
3	*n*-Heptyl (1.5 equiv)		rt	16 h	**9c** (88)
4	Benzyl (1.5 equiv)		Reflux	16 h	**9d** (83)
5	*i*-Propyl (2 equiv)		Reflux	16 h	**9e** (83)
6	Cyclohexyl (2 equiv)		Reflux	72 h	**9f** (75)
7	(*R*)-Methylbenzyl (1.5 equiv)		Reflux	5 d	**9g** (0)
8	Phenyl (3 equiv)[a]	DIEA (3.3 equiv)	Reflux	72 h	**9h** (67)
9	*p*-MeOphenyl (3 equiv)[a]	DIEA (3.3 equiv)	Reflux	72 h	**9i** (58)
10	*m*-MeOphenyl (3 equiv)[a]	DIEA (3.3 equiv)	Reflux	24 h	**9j** (27)
11	*p*-PheOphenyl (3 equiv)[a]	DIEA (3.3 equiv)	Reflux	24 h	**9k** (35)

[a] R–NH_2 as hydrochloride form.
[b] Isolated yield.

Table 2. Trans-alkoxylation reaction **15**→**16a–e**

Entry	ROH	Conditions	Product (Yield %)
1	EtOH	Reflux, 2 h	**16a** (100)
2	*n*-BuOH	Reflux, 2 h	**16b** (100)
3	*i*-PrOH	Reflux, 2 h	**16c** (100)
4	*t*-BuOH	Reflux, 3 h	**9g** (100)
5	BnOH	100 °C, 48 h	**16d** (69)
6	PhOH	100 °C, 48 h	**16e** (21)

cyanate which was immediately trapped with (*R*)-methylbenzylamine to give product **14** in 51% overall isolated yield. Condensation of ammonia at −72 °C in the mixture of thiourea **14**, EDCI and DIEA in dichloromethane gave the desired compound **15** in 73% yield (Scheme 4).

To our delight, by the Troc cleavage procedure of *N*-alkyl-*N*′-Troc-guanidine under the classical conditions (Zn, EtOH),[11] urethane **16a** was obtained cleanly and quantitatively.

Wondering whether the zinc is playing any role, the reaction was carried out solely in refluxing alcohol. The substitution of the Troc group by any alkoxy group was found to be rather general, since all the tested alcohols formed the substitution product (Table 2).

Importantly, the reaction with the bulky *t*-BuOH underwent the formation of the desired compound *N*-methylbenzyl-*N*′-Boc guanidine **9g** in quantitative yield (entry 4). Reaction with the poorly nucleophilic phenol gave the lowest yield (entry 6).

A similar trans-alkoxylation in an intramolecular reaction which led to a cyclic urethane was observed by Schmidt and co-workers[12] A Mitsunobu O-alkylation of Fmoc-guanidines with alcohols was also reported.[13]

In conclusion, we have found that the monoprotected Boc-1*H*-pyrazole-1-carboxamidine can be conveniently employed for the synthesis of *N*-alkyl-*N*′-Boc guanidine by reaction with unhindered primary amines. Synthesis of (*R*)-*N*-methylbenzyl-*N*′-Troc guanidine was achieved through an isothiocyanate pathway. Transformation of the Troc group into other carbamate groups (e.g., Boc, Cbz) was simply achieved by refluxing in the appropriate alcohol. Further development of this reaction including solid phase and asymmetric synthesis are under progress.

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8. Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (s, 9H), 5.23 (s, 2H), 6.31 (dd, $J = 1.5$ and 2.7 Hz, 1H), 7.23 (m, 5H), 7.52 (br s, 1H), 8.23 (d, $J = 2.7$ Hz, 1H), 9.01 (br s, 1H). Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (s, 9H), 1.57 (s, 9H), 6.44 (dd, $J = 2.7$ and 1.7 Hz, 1H), 7.64 (d, $J = 1.7$ Hz, 1H), 8.32 (d, $J = 2.7$ Hz, 1H), 8.94 (br s, 1H). See Ref.: Drake, B.; Patek, M.; Lebl, M. *Synthesis* **1994**, 579–582.
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