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Preparation of *N,N'*-Bis(aryl)guanidines from Electron Deficient Amines Via Masked Carbodiimides

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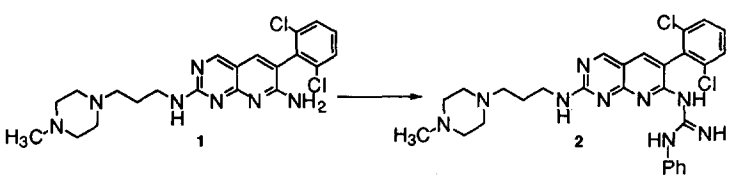
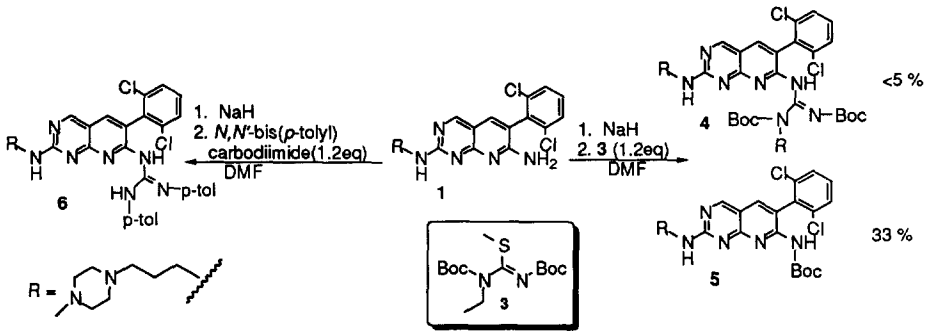
Abstract: Preparation of *N,N'*-bis(aryl)guanidines by alkylation of electron deficient amines with trityl protected carbodiimides is described. Also reported is a method for the dehydration of *N*-trityl-*N'*-aryl ureas to the corresponding carbodiimides using the Burgess reagent. © 1997 Elsevier Science Ltd.

The classical preparation of *N,N'*-bis(aryl)guanidines involves alkylation of an amine with an appropriately substituted urea or thiourea derivative in the presence of a heavy metal catalyst.[1] More recently, derivatized pseudourea reagents have been reported including aminoiminomethanesulfonic acids,[2a] cyanimides,[2b] carboxamidines[2c] and chloroformamidines.[2d] While there are numerous examples employing these reagents, few show promise with electron deficient amines. Carbodiimides have also been used for the preparation of guanidines, however, a general route to prepare disubstituted guanidines from highly functionalized electron poor amines has not been developed.[3] During a recent program to develop tyrosine kinase inhibitors, we required a method to convert substituted pyridopyrimidine derivative **1** to the disubstituted guanidine, **2**.[4] Herein, we report the preparation of **2** using a masked carbodiimide prepared under mild conditions.



We found that **1** was unreactive towards common guanylating reagents. This is consistent with our previous experience with **1**, in that acylation of the primary amino function requires generation of the sodium salt with NaH in DMF or dioxane. A protected guanylating reagent is required to apply a similar strategy to prepare **2**. Unexpectedly, we found that the reaction of **1** with sodium hydride followed by treatment with *N,N"*-bis(Boc)-*N*-ethyl-*S*-methyl isothiourea[5] (**3**) afforded less than 5% of the protected guanidine **4** (Scheme 1).[6] The major product of this reaction was assigned as the *N*-Boc compound (**5**), isolated in 33% yield. We then chose to investigate carbodiimides as less hindered and more reactive guanylating reagents. Treatment of **1** with NaH followed by *N,N'*-bis(*p*-tolyl)carbodiimide gave guanidine **6** in 64% yield (Scheme 1). Based on this observation, we felt that preparation of an *N*-protected carbodiimide would provide a vehicle to prepare **2**.

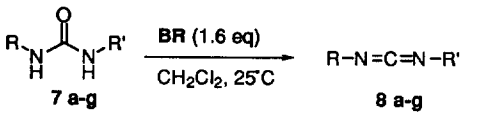


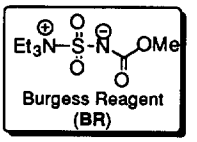
Scheme 1

Recently, it was reported that Burgess reagent (BR) can be used in the conversion of primary amides to nitriles.[7] We chose to apply this reagent to the conversion of ureas to carbodiimides after considering the similarities between the two reactions. Additionally, the by-products of BR are either water soluble or volatile, subsequently simplifying isolation of the carbodiimide. Indeed, TLC analysis of the reaction of *N*-methyl-*N'*-phenyl urea (**7a**) with BR (1.6 eq.) in dichloromethane indicated complete conversion to the diimide (**8a**) in 20 h (Table 1). Diimide **8a** was isolated in 45% yield and >95% purity without chromatography or distillation.[8] In route to a masked diimide, we chose to prepare *N*-phenyl-*N'*-trityl urea (**7b**) and effect dehydration using BR. Again, complete conversion to the desired diimide (**8b**) was observed in 20 h. While these conditions proved general for examples **7a-g**, simple alkyl substituted ureas (**7 h-i**) afforded only starting material on extended reaction with BR (Table 1).[9]

Carbodiimide **8b** was used to prepare trisubstituted guanidine **9** via alkylation of sodium salt of **1** in DMF (Scheme 2). Surprisingly, the trityl group was resistent to cleavage in either TFA/CH_2Cl_2 or dilute HCl in anhydrous MeOH. The desired product (**2**) was obtained using 4 N HCl in 2-propanol for 36 h[4]. The truncated analog (**10**) was prepared from 2-aminopyridine to investigate the sluggishness of the trityl cleavage reaction (Scheme 3).[10] On exposure to 4 N HCl in 2-propanol, complete conversion to the disubstituted guanidine (**11**) was achieved in less than two hours.[11] This discrepancy in reactivity may indicate that hydrolysis is slowed by the polycationic nature of **9** in acidic media.

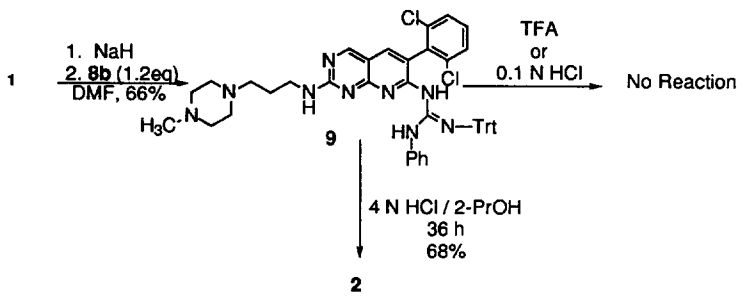
Table 1. Preparation and Characterization of Carbodiimides from Ureas Using Burgess Reagent



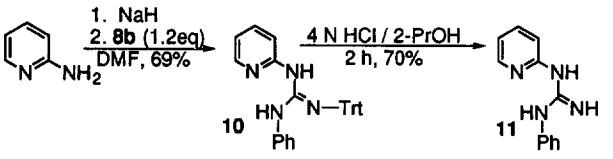


Urea	R	R'	Diimide	Yield (%)	IR (cm^{-1})
7a	Ph	Me	**8a**	45	2121
7b	Ph	Trityl	**8b**	90	2128
7c	3-NO_2 Ph	Trityl	**8c**	85	2123
7d	2-Cl Ph	Trityl	**8d**	91	2140
7e	4-F Ph	Trityl	**8e**	82	2139
7f	Ph	4-OMe benzyl	**8f**	85%	2128
7g	Ph	3,4-$(OMe)_2$ benzyl	**8g**	91%	2124
7h	2-Pr	Trityl	--	0%	ND
7i	Et	Trityl	--	0%	ND

ND-not determined



Scheme 2



Scheme 3

In conclusion, we have developed a method to prepare *N,N'*-bis(aryl)guanidines from highly electron deficient amines. We have also described a mild method for preparation of masked aryl carbodiimides using Burgess reagent via a procedure which allows isolation of novel carbodiimides without distillation or chromatography. Efforts to broaden the scope of this strategy to include alkyl substituted congeners are in progress.

REFERENCES AND NOTES

1. a) Kim, K. S.; Ligang, Q. *Tetrahedron Lett.*, **1993**, *34*, 7195. b) Kent, D. R.; Cody, W. L.; Doherty, A. M.*Tetrahedron Lett.*, **1996**, *37*, 8711. c) Kim, K. S.; Ligang, Q.*Tetrahedron Lett.*, **1993**, *34*, 7677.

2. For examples see: a) McAlpine, I. J.; Armstrong, R. W. *J. Org. Chem.*, **1996**, *61*, 5674. Nakayama, T.; Taira, S.; Ikeda, M.; Ashizawa, H.; Oda, M.; Akara, K.; Fujii, S. *Chem. Pharm. Bull.* **1993**, *41*, 117. b) Kim, Y. H.; Yon, G. H. *J. Chem. Soc. Commun.*, **1983**, 715. Maryanoff, C. A.; Stanizone, R. C.; Plampin, J. N.; Mills, J. E. *Org. Chem.*, **1986**, *51*, 1882 c) Bernatowicz, M. S.; Wu, S.; Matsueda, G. R. *Tetrahedron Lett.*, **1993**, *34*, 3389 d) Nagaran, S.; Ho, T. L.; DuBois, G. E. *Synth. Comm.*, **1992**, *22*, 1191.

3. Mikolajczyk, M.; Kielbaskinski, P. *Tetrahedron Lett.* **1981**, *37*, 233.

4. Schroeder, M. C.; Hamby, J. M.; Gohar, P. J.; Winters, R. T .; Connolly, C. J. C.; Showalter, H. D . H.; Kraker, A. J.; Amar, A.; Shen, C.; Lu, G. H.; Daharing, T. A.; Panek, R. L.; Major, T. C.; Doherty, A. M. Synthesis and SAR Pyrido[2,3-d]Pyrimidine- 2-7-Diamines in the Development of Potent Water Soluble Tyrosine Kinase Inhibitors. 25th National Medicinal Chemistry Meeting, Ann Arbor, MI June 18-21 1996.

5. Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z.*Tetrahedron Lett.* **1992**, *33*, 5933. Lammin, S. G.; Pedfrift, B. L.; Ratcliffe, A. J. *Tetrahedron Lett.* **1996**, *37*, 6815.

6. All new compounds afforded consistent characterization.

7. Claremont, D. A.; Phillips, B. T. *Tetrahedron Lett.* **1988**, *29*, 7195.

8. A representative procedure: To a suspension of **7b** (3.0 mmol, 1.13 g) in CH_2Cl_2 (12 mL), was added Burgess reagent (1.52g, 6.4 mmol). After stirring for 20 h, the mixture was diluted with CH_2Cl_2 (25 mL) and extracted with cold water (15 mL), dried and concentrated. The residue was dissolved in a minimum amount of ethyl acetate (1 mL) and diluted 15-fold with hexanes. The resulting suspension was filtered and concentrated to afford **8b** (980 mg, 90 %) as a colorless oil which was used without further purification. ^{1}H NMR ($CDCl_3$): 7.25 (d, *J*= 7.3 Hz, 2H), 7.07 (dd, *J*= 7.3, 7.3 Hz, 3H), 3.11 (s, 3H). IR (KBr) 3469, 2930, 2854, 2120, 1449, 1359, 1345, 1345.

9. A similar observation was made using di-2-pyridyl thionocarbonate as a dehydrating agent: *Tetrahedron Lett.*, **1985**, *26*, 1161.

10. N-Phenyl-N'-(2-aminopyridyl)-N''-trityl guanidine (**10**). 2-Aminopyridine (80 mg, 1.0 mmol) was added to a stirred supension of NaH (60 % suspension in oil, 44 mg, 1.1 mmol) in anhydrous DMF (2 mL). After 5 min, a solution of **8b** (360 mg, 1.0 mmol) in DMF (2 mL) was added dropwise over 5 min. After stirring 2 h, the reaction was diluted with aqueous NH_4Cl (10 mL), extracted with ethyl acetate, dried and concentrated. Guanidine **10** (304 mg, 70%) was isolated via column chromatography (EtOAc / Hexane; 1:1) as a white foam. Mp: 87-91 °C. ^{1}H NMR ($CDCl_3$): 12.70 (s (bd), 1H), 8.05 (dd, 5.0, 1.2 Hz), 7.6-6.8 (m, 23H). CIMS *m/z* (rel int): 454 (15), 455 (11), 456 (3), 457 (0.5), 243 (100). IR (KBr): 3406, 3056, 2923, 2852, 1631, 1586, 1546, 1435. Anal. Calcd for $C_{31}H_{26}N_4$: C, 81.91; H, 5.77; N, 12.32. Found: C, 81.95; H, 5.92; N, 12.06.

11. N-Phenyl-N'-(2-aminopyridyl) guanidine (**11**). Protected guanidine **10** was added to a solution of HCl in 2-propanol (4N, 2.0 mL). After stirring for 2 h the solvent was removed and the residue was recrystallized form 2-propanol to afford **11** as the dihydrochloride salt. Mp: >250 °C. ^{1}H NMR (D_2O): 8.18 (d, *J*=5.2 Hz, 1H), 7.73 (dd, *J*=6.3, 6.4 Hz, 1H), 7.41-7.22 (m, 5H), 7.08 (dd, *J*=7.1, 6.6 Hz, 1H), 6.96 (d, *J*=8.3 Hz, 1H). APCI*m/z* (rel int): 213 (100), 214 (12), 215 (1). IR (KBr): 3059 (bd), 3056, 1669, 1641, 1595, 1571, 1486, 1232. Anal. Calcd for $C_{12}H_{14}N_4 \cdot 2.25$ HCl: C, 48.65; H, 5.53; N, 18.91. Found: C, 43.64; H, 5.37; N, 18.62.

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