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PRELIMINARY COMMUNICATION

Solid Support-Bound Synthesis of Polyfunctional Unsymmetrical Ureas

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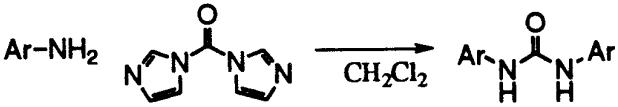
Solid support-bound chemistry has been used to gain access to several polyfunctional ureas which could not be easily produced via traditional solution phase approaches.

In conjunction with our work on the computer aided design of novel inhibitors of therapeutically important enzyme targets, we required a route to both symmetrical and unsymmetrical ureas and diamides containing several potentially reactive functional groups. We wished to develop a route for the rapid synthesis of a large number of analogs which did not require numerous protection and subsequent deprotection steps.

Initially, coupling two aromatic amines through the use of carbonyl diimidazole (CDI) (*1*) (Eq. [1]) allowed for the formation of several multifunctional symmetrical ureas (Fig. 1, compounds **1–3**). This method could be expanded to other urea analogs, including the thiourea (**4**) and oxalyl functionalities (**5**), by use of the appropriate diimidazole species. However, this method was not sufficiently general to be used if multiple functional groups had competitive reactivity, and it also did not permit access to unsymmetrical compounds.



[1]

As an alternative, the solution phase two-step procedure shown in Scheme 1 was attempted (*2*). While this procedure did allow the formation of trace quantities of unsymmetrical urea products, they were highly contaminated by side products and required extensive purification, which was complicated by the extremely polar nature of our desired products.

In order to avoid these difficulties, we decided to use a solid support bound procedure to produce the required unsymmetrical multifunctional ureas (*3*) (Scheme 2). Typically, the use of a solid support allows the use of large excesses of reagents while simplifying the purification process by allowing these excess reagents and solution phase side products to be removed by simple filtration.

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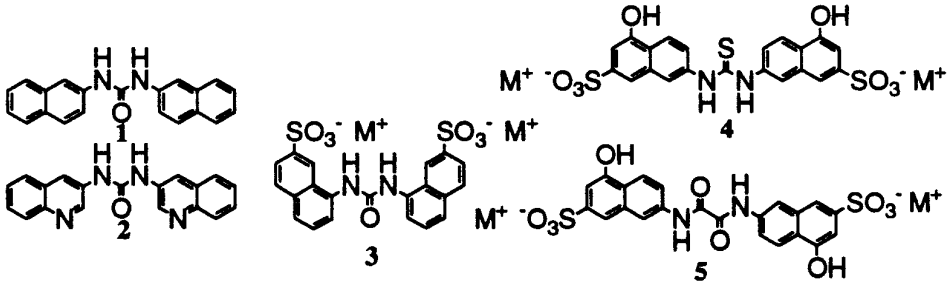
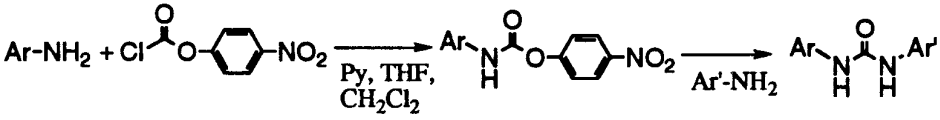


FIG. 1. Examples of symmetrical ureas and urea analogs accessible by acid imidazole coupling procedure. M^+ = sodium or imidazolium salt.

Initial loading studies of the 2-chlorotrityl resin (*4*, *5*) showed that 9-fluorenylmethanolcarbamate (FMOC)-protected J-acid (**6**), did not load effectively onto the resin, presumably due to steric hindrance. Traditional Merrified resins were not tested as cleavage of the anticipated products was expected to require excessively harsh conditions. Several groups have used resins with a hydroxy group to which they bound a carboxylic acid via an ester linkage (*6*). While our desired starting material 7-amino-4-hydroxy-2-naphthalenesulfonic acid does not contain a carboxylic acid, we decided to use this form of linkage by using a carboxy resin and forming our linkage to the phenol of our primary starting material in a procedure similar to that used by Meyers (*7*) for much less polar materials. Carboxy-polystyrene resin (molar substitution = 0.66 mmol/g) is loaded with FMOC-protected J-acid (**6**) following the procedure of Meyers (*7*) for the loading of phenols. At this point the loaded polymer may be pumped dry and stored if desired for up to several weeks. While the traditional deprotection of the FMOC group with piperidine cleaves the ester linkage to the resin, the FMOC group is conveniently removed by treatment with DMF/TEA (dimethylformamide/triethylamine, 4/1 (v/v)) for 3 h. The reaction mixture is filtered under argon and washed with dry CH_2Cl_2. The polymer is solvated in a mixture of dry CH_2Cl_2 (4 ml) and CDI (carbonyl diimidazole, approximately 15 eq.). This mixture is shaken for 12–24 h and then filtered under argon to remove the majority of any remaining excess CDI. If the next aniline to be coupled has more than one potentially reactive functional group, as is the case when making a urea from a diaminoaryl species or aminophenols in which both amino and phenol functionalities are of comparable reactivity, the polymer should be washed with dry CH_2Cl_2 to remove excess CDI. A solution of amine in dry



SCHEME 1