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Solid-Supported Chloro[1,3,5]triazine. A Versatile New Synthetic Auxiliary for the Synthesis of Amide Libraries

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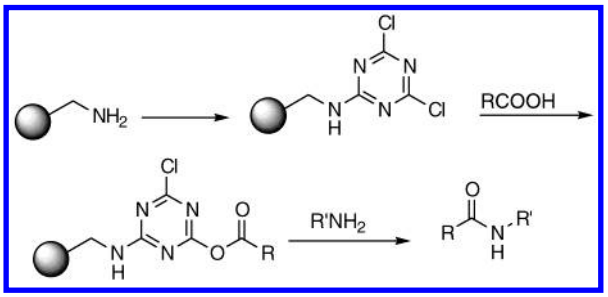
ABSTRACT



2,4,6-Trichloro[1,3,5]triazine was loaded on different types of NH_2–functionalized resins to give a new supported reagent. The best results, in term of yields products, were obtained using the chlorotriazine linked to a polystyrene–poly(ethylene glycol) resin. This reagent was employed for the solution-phase synthesis of different amides and dipeptides.

Polymer-supported reagents and auxiliaries have found increasing applications for the preparation of small organic molecules during the past few years.[1] Recent advances in the development of new solid-supported reagents[2] have opened new routes to library synthesis in the solution phase with the aim of implementing the protocol with robotic systems.

Among several polymeric reagents described, supported *N*-hydroxybenzotriazole[3] and differently substituted carbodiimides[4] have been prepared and used for the formation of amides, lactames, and related reactions.[5]

Although very effective, these reagents must be synthesized on the resin in a multistep procedure.[3,6] In the few cases of commercially available immobilized reagents, the resins are expensive and rather sensitive to prolonged storage.[7]

Following our interest in the chemistry of triazine derivatives,[8] we speculated on the possibility of using a resin-bound triazine to activate a carboxylic acid for a nucleophilic substitution at the carbonyl to give an amide or a derivative. 2,4,6-Trichloro[1,3,5]triazine and 2-chloro-4,6-dimethoxy-[1,3,5]triazine are know to be versatile and selective coupling reagents for amide synthesis.[9] The chlorotriazine is generally activated with *N*-methylmorpholine (NMM) to give a mor-

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(6) Kalir, R.; Warshawsky, A. Fridkin, M.; Patchornik, A. *Eur. J. Biochem.* **1975**, *59*, 55.
(7) The polymer-supported bis(6-carboxy-HOBt)-*N*-(2-aminoethyl)aminomethyl polystyrene and *N*-cyclohexylcarbodiimide *N*′-methyl polystyrene are now available from Novabiochem, catalog no. 01-64-0179 and 01-64-0211.
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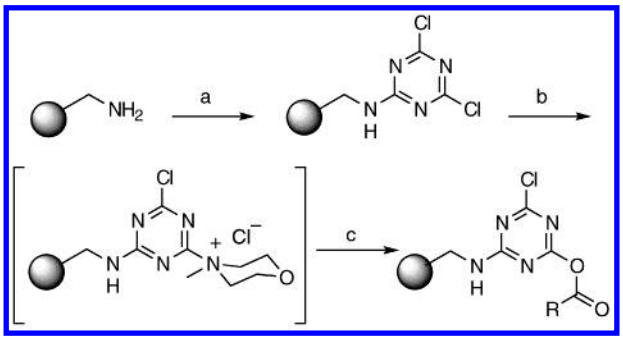
pholinium salt that reacts with a carboxylic acid to generate the activated ester. This ester is relatively stable to oxygen nucleophiles but reacts easily with amines to give high yields of the corresponding amides.[10]

Thus we attempted to anchor 2,4,6-trichloro[1,3,5]triazine **1** onto a polystyrene resin using commercially available substrates. A Wang type resin loaded with Fmoc-Gly (1.0 mmol/g resin) was used as starting material. After deprotection of the Fmoc under standard conditions, the NH_2 on the resin was treated with a THF solution of **1** (5 equiv) in the presence of DIPEA (Scheme 1). The reaction occurred

Scheme 1[a]



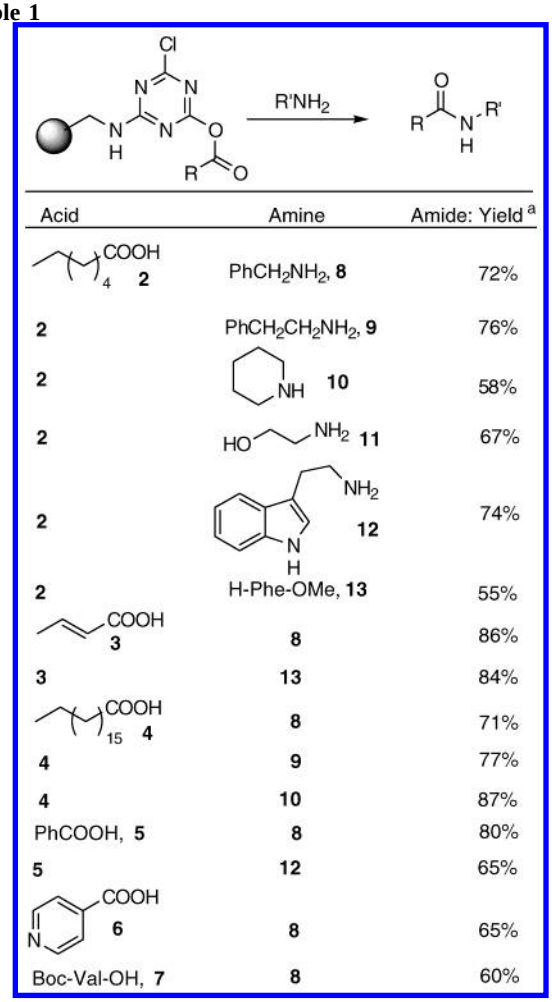
[a] (a) (1), DIPEA, THF; (b) NMM, THF; (c) RCOOH, THF.

within 10 min as showed by a negative ninhydrine test.[11] After washing several times with THF, the resin was dried and could be stored at 4 °C for several days. Alternatively the resin was mixed with THF and the loaded chlorotriazine activated with a THF solution of NMM (1.5 equiv with respect to the theoretical loading). After few minutes, a solution of the carboxylic acid (2 equiv with respect to the loading) in THF was added and the mixture stirred for 3 h under a nitrogen stream in a vial equipped with a sintered glass plate. The excess of the acid and the salts eventually formed were washed away with THF and DMF. The resin loaded with the activated carboxylate can be dried and stored for further applications as, for example, splitting into different vials for a parallel synthesis.[12]

The resin, loaded with the appropriate carboxylic acid, was treated with a THF solution of the amine (1.2 equiv) in the presence of 1 equiv of NMM.[13] The conversion of the reaction was monitored by TLC or GC. At the end (3 h was generally a long enough reaction time for a high conversion) the product was recovered by filtration on the sintered glass plate, followed by elimination of the excess of amine by acidic workup[14] and evaporation of the solvent.

Following this protocol, the synthesis of a variety of amides was accomplished as reported in Table 1.

Table 1



Acid	Amine	Amide: Yield[a]
COOH (4) **2**	$PhCH_2NH_2$, **8**	72%
2	$PhCH_2CH_2NH_2$, **9**	76%
2	NH **10**	58%
2	HO, NH_2 **11**	67%
2	NH_2, N H **12**	74%
2	H-Phe-OMe, **13**	55%
COOH **3**	**8**	86%
3	**13**	84%
COOH (15) **4**	**8**	71%
4	**9**	77%
4	**10**	87%
PhCOOH, **5**	**8**	80%
5	**12**	65%
COOH, N **6**	**8**	65%
Boc-Val-OH, **7**	**8**	60%

[a] Yields of isolated and fully characterized products. The ^1H NMR analysis of the crude compounds showed the presence 5−10% of byproducts.

We chose a series of representative aliphatic and aromatic carboxylic acids with different properties and a series of simple primary and secondary amines. We observed that the reaction always gave good yields of the desired products even when using a lipophilic acid as **4**. Isonicotinic acid **6** was analogously transformed into the amide with an extremely simple procedure in comparison to the methods generally employed with this kind of acid. Acceptable results were

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(11) The correct loading of **1** on the resin (one triazine ring for one amino group) was confirmed by the contents of Cl and N determined by microanalysis.

(12) The selective substitution of one single chlorine with the carboxylate was verified by FT-IR analysis of the beads and by micronalysis.

(13) The presence of NMM in the reaction is necessary. Attempts to use less than 1 equiv of the desired amine and to obtain a solution of the pure product at the end of the reaction were unsuccessfull (in our hands).

(14) The classical two-phase extraction with an acidic aqueous solution can be substituted by a passage of the THF solution, coming from the vial, through a small column filled with an acidic ion-exchange resin. After this treatment the amide could be recovered by evaporation of the solvent with an acceptable level of purity. See: Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 513.

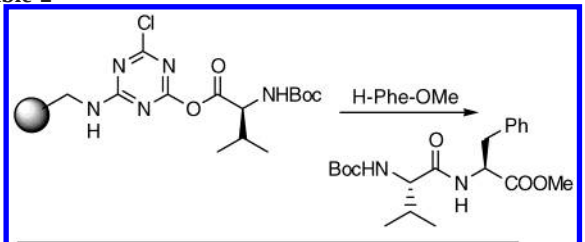
obtained with amino acid **7**. Among the amine used, it is noteworthy to see that tryptamine **12** or unprotected ethanol amine **11** afforded the corresponding amides in good yields.

The triazine loaded on the Wang-Gly resin displayed good reactivity in THF or CH_2Cl_2, solvents that are easy to remove after the reaction and allow for easy isolation of the products. Nevertheless, when the amine was insoluble in these solvent (as **12**), 1-methyl-2-pyrolidinone (NMP) was successfully employed.

When we tried to use the triazine loaded on the Wang resin for the preparation of a dipeptide, (Boc-Val-OH and H-Phe-OMe), we observed low yields (50%) and the presence of impurities.

With the aim of improving the yields of the amide, we explored different possibilities and discovered that the nature of the polymer employed influenced the results. In Table 2

Table 2



Starting resin employed	Yield[a]
Polystyrene-CH_2-NH_2	25%[b]
Wang-$OOCCH_2NH_2$	64%
Merrifield-$OOCCH_2NH_2$	51%
Polystyrene-PEG-NH_2	95%

[a] HPLC analysis of the peptide showed less than 5% of racemization. [b] The low yield is due to an uncomplete loading of the triazine on the resin.

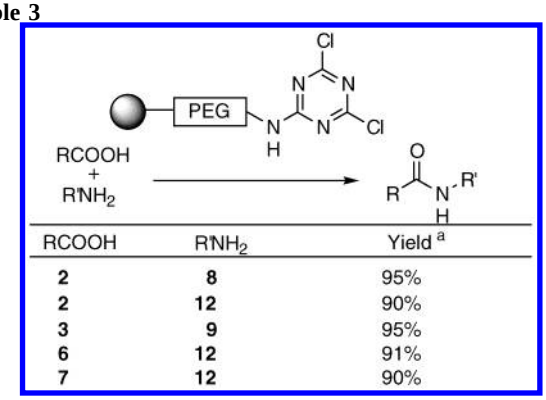
are reported the yields of the reaction of formation of the dipeptide Boc-Val-PheOMe using the chlorotriazine loaded on different resins.

The cross-linked polystyrene−poly(ethylene glycol) system is more flexible and can accommodate the reagent far away from the beads, improving the reactivity of the activated ester that is probably hindered by the groups that remain close to the carbonyl on the surface of the resin.

The results of some selected couplings carried out with the triazine loaded on the polystyrene-PEG-CH_2-NH_2 resin are reported in Table 3.

In conclusion we have described an effective method for the preparation of a supported coupling reagent starting from

Table 3



RCOOH	R'NH_2	Yield [a]
2	**8**	95%
2	**12**	90%
3	**9**	95%
6	**12**	91%
7	**12**	90%

[a] Yields of isolated and fully characterized products. The purity of the products was always about 95% (^{1}H NMR 300 MHz).

a terminal NH_2 resin that can be successfully used to prepare libraries of amides (or peptides) in solution employing volatile solvents. The loading is possible on several kinds of commercially available resins and can be done just before use. This feature if particularly important as the applications of the reagent can be expanded to different resins with swelling properties more appropriate to the solvent required in the reaction. Moreover the reagent employed (**1**) has no cost when compared with the resin price and can be used without any additional auxiliary (DCC or PyBOP are required in the case of supported HOBt).[3] The supported reagent is stable for days in dry form, and the corresponding activated ester can be stored in an anhydrous atmosphere for at least 1 week without any appreciable modification of the reactivity. Finally, although we did not try, the resin could be recycled at the end of the reaction.[15]

We are currently using this reagent for the derivatization of biologically active amines, as a scavenger for primary amines, and for the preparation of a small molecule amide library.

Acknowledgment. Support has been provided by the MURST (Rome) within the Progetti di Ricerca di Rilevante Interesse Nazionale—Chimica dei Composti di Interesse Biologico-Es Fin. 1997.

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