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Development of new acid-functionalized resins for combinatorial synthesis on solid supports†

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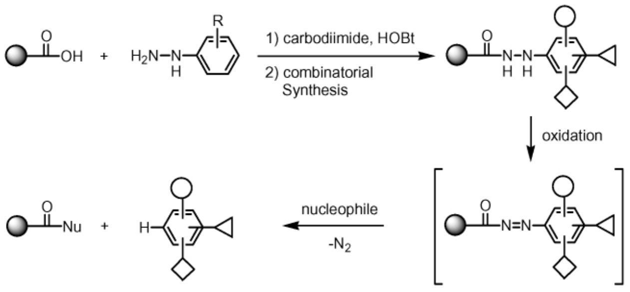
New methods for the synthesis of acid-functionalized polystyrene and TentaGel resins are described; these methods serve to overcome problems with currently available resins and will be instrumental in spurring the use of carboxylic acid resins in solid phase chemistry.

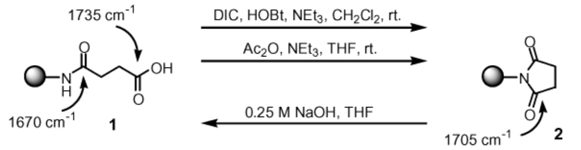
Paramount to the success of combinatorial chemistry is the availability of different polymeric supports carrying suitable functional groups which allow for facile attachment of starting material. Such supports should be stable under a broad variety of reaction conditions and finally release the synthesis products under mild conditions. From the various resins available for this purpose polymeric supports carrying carboxylic acids on their surface are regularly used for attachment of alcohols and amines.[1] In the development of the traceless hydrazide linker group[2] we required such a resin to couple different hydrazines to the solid support before subjecting them to combinatorial derivatization and final oxidative traceless cleavage (Scheme 1).

The initial phase of this investigation was severely complicated by non-reproducible results, which were traced to problems arising during the attachment of the hydrazines to the carboxylic acid-functionalized solid support. Thus, Fourier transform IR spectroscopic inspection of the resins obtained after activation of the polymer-bound carboxylate with carbodiimide and subsequent treatment with different phenylhydrazines consistently revealed a strong band at 1705 cm^{-1} which could not be ascribed to the starting material or the product. The commercially available resins employed in these experiments (polystyrene and TentaGel, Rapp Polymere) were obtained from an amino-functionalized carrier by formation of a succinic acid monoamide, *i.e.* they embody an amide nitrogen and an activatable carboxylic acid in a distance suitable for formation of a five-membered ring imide. Thus, in order to explain the finding detailed above it was speculated that after reaction of the carboxylic acid **1** with the carbodiimide the activated intermediate is attacked intramolecularly by the nitrogen of the amide group to finally give rise to polymer-bound cyclic imide **2** (Scheme 2).

Such cyclizations are well-known in solution.[3,4] Formation of imide **2** was readily induced in model reactions either by treatment of carboxy-functionalized resin **1** with a carbodiimide or with acetic anhydride (Scheme 2). In both cases the FT-IR spectrum of resin **2** displayed a strong peak at 1705 cm^{-1}. Under basic conditions the polymer-bound succinimide was readily hydrolyzed to give acid **1**. These findings are of general relevance since they point to problems that may arise if commercially available polymeric resins carrying a linker of the type found in **1** are used. They also call for the development of alternative carboxylic acid functionalized supports which do not undergo this undesired side reaction.



Scheme 1 Concept of the traceless phenylhydrazide linker.



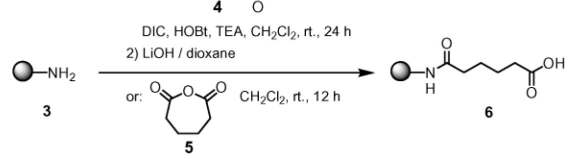
Scheme 2 Observed intramolecular imide formation on solid support.

In attempting to overcome this problem we reasoned that an elongation of the carbon chain by two methylene units, *i.e.* the use of an adipic acid derivative instead of a succinic acid derivative, might provide a straightforward solution since the formation of a seven-membered ring is unfavourable.

Consequently, different amino resins (polystyrene-NH_2, TentaGel-NH_2, ArgoPore-NH_2) were treated with adipic acid dichloride in dichloromethane and pyridine followed by aqueous work-up. The acid-functionalized resins obtained thereby did not undergo the undesired cyclization upon activation with carbodiimide and they performed well in a series of transformations employing the traceless hydrazide linkers, *i.e.* Pd-catalyzed CC-bond formations and reductive amination reactions.[2a] However, the acylation with the dichloride also resulted in substantial cross-linking of amino groups of the starting material and the level of product loading amounted only up to 40% of the original loading with amino groups.

This situation was significantly improved if freshly prepared[5] adipic acid anhydride **5** was employed or if first an adipic acid monoamide was formed with adipic acid methyl ester **4** followed by basic saponification of the ester group (Scheme 3).

Analysis of the coupling efficiency by means of the Kaiser test[6] which detects remaining free amino groups revealed that essentially no underivatized amino groups had remained. The loading level was then determined by nucleophilic esterification of the carboxylic acid groups with 2-methoxy-5-nitrobenzyl bromide in DMF and basic saponification of the resulting



Scheme 3 Synthesis of adipic acid functionalized resin **6**.

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b204423d/

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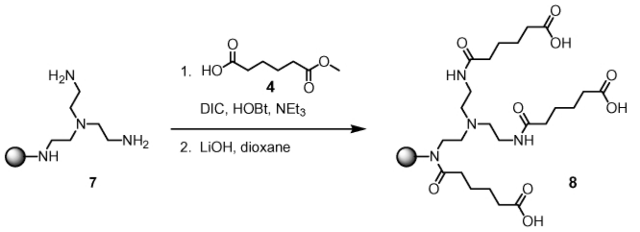
polymeric esters. The loading was quantified by determining the amount of released 2-methoxy-5-nitrobenzyl alcohol by means of UV spectroscopy (at 307 nm).[7] These determinations revealed that derivatization of polystyrene-NH_2 (loading level: 1.1 mmol g^{-1}), TentaGel-NH_2 (loading level: 0.42 mmol g^{-1}) and ArgoPore-NH_2 (loading level: 1.13 mmol g^{-1}) had proceeded with yields in the range of 93–98%.

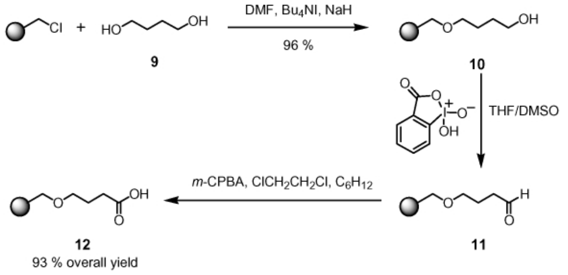
A polymer with particularly high loading capacity was obtained from tris(2-aminoethyl)amine resin **7** (Scheme 4).[8]



Scheme 4 Preparation of a high-loading acid functionalized resin.

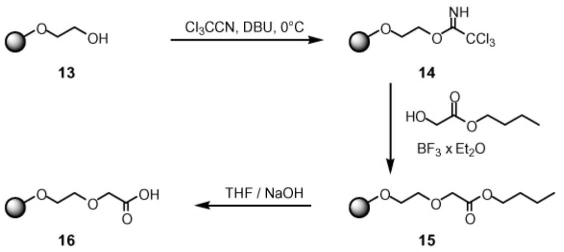
This polymer belongs to the polyamine resins which usually are employed as acid scavengers in liquid phase reactions.[9] The two-step process composed of carbodiimide-mediated amide bond formation and hydrolysis under basic conditions gave rise to an acid-functionalized polymeric support with a loading of 1.66 mmol g^{-1}.

All the acid-functionalized resins described above embody an amide group. While this function does not interfere with many organic transformations it would be highly desirable to have an alternative with a different linkage. To this end, resins were synthesized in which the carboxylic acid linker is attached to the solid support *via* an ether bond. In initial experiments the reaction of chloromethyl polystyrene with the sodium salt of glycolic acid *n*-butyl ester was investigated. After deprotonation of the alcohol with NaH and subsequent treatment of the chloromethylated polymer with 5 equiv. of the resulting sodium salt in the presence of tetrabutylammonium iodide for 48 h the conversion only reached 47–67%. As an alternative butanediol **9** was employed as nucleophile and the resulting polymer bound alcohol **10** was oxidized in two steps first to the aldehyde **11** (employing 1-hydroxy-1,2-benziodoxol-3(*1*H)-one (IBX)) and then to the acid **12** (employing *m*-CPBA; see Scheme 5), which was formed with an overall yield of 93%. The loading of polymeric support **10** was determined by acylation with Fmoc-Cl, cleavage of the urethane and UV-spectrometric determination of the released fulvene.[10] The loading of resin **12** was determined as described above for polymeric support **6**. Under the conditions shown in Scheme 5 only minor cross-linking occurred. This is remarkable since the resin used was highly loaded (1.1 mmol g^{-1}; Rapp Polymere).



Scheme 5 Synthesis of an acid-functionalized polystyrene resin with an ether linkage.

Finally, an acid-functionalized TentaGel resin was prepared from the corresponding alcohol **13** (Rapp Polymere, loading 0.41 mmol g^{-1}) by means of an intermediate trichloroacetimidate according to Hanessian *et al.*[11] To this end, resin **13** was treated with Cl_3CCN in the presence of DBU to yield intermediate **14** which was converted to ether **15** (Scheme 6).



Scheme 6 Synthesis of an acid-functionalized TentaGel resin with an ether linkage.

Finally, the ester group was saponified to yield desired acid **16**. After repeating this sequence of transformations two times the loading level of acid resin **16** was determined to be 0.34 mmol g^{-1}, *i.e.* the overall yield was 84%.

In conclusion we have developed several methods for the synthesis of different acid-functionalized polymeric resins. These methods serve to overcome undesired and unexpected problems which may occur during the activation of some of the commercially available acid-functionalized polymeric supports. They should be instrumental in spurring the use of carboxylic acid resins in solid phase chemistry.[12]

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Notes and references

1 F. Z. Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, 2000.
2 (*a*) F. Stieber, U. Grether and H. Waldmann, *Angew. Chem.*, 1999, **111**, 1142–1145; F. Stieber, U. Grether and H. Waldmann, *Angew. Chem., Int. Ed.*, 1999, **38**, 1073–1077; (*b*) C. Rosenbaum and H. Waldmann, *Tetrahedron Lett.*, 2001, **42**, 5677–5680.
3 W. Flitsch and P. Russkamp, *Liebigs Ann.*, 1985, **7**, 1398–1412.
4 (*a*) K. Kamaike, M. Takahashi, K. Utsugi, K. Tomizuka and Y. Ishido, *Tetrahedron Lett.*, 1995, **36**, 91–94; (*b*) J. H. Musser, D. M. Kubrak, J. Chang, S. M. DiZio, M. Hite, J. M. Hand and A. J. Lewis, *J. Med. Chem. 1987, 30*, 1987, **30**, 400–405.
5 W. Mormann, S. Hoffmann and W. Hoffmann, *Chem. Ber.*, 1987, **120**, 285–290.
6 E. Kaiser, R. L. Colescott, C. D. Bossinger and P. I. Cook, *Anal. Biochem.*, 1970, **34**, 595–598.
7 U. Grether and H. Waldmann, *Chem. Eur. J.*, 2001, **7**, 959–971.
8 R. J. Booth and J. C. Hodges, *J. Am. Chem. Soc.*, 1997, **119**, 4882–4886.
9 (*a*) C. Blackburn, B. Guan, P. Fleming, K. Shiosaki and S. Tsai, *Tetrahedron Lett.*, 1998, **39**, 3635–3638; (*b*) M. W. Creswell, G. L. Bolton, J. C. Hodges and M. Meppen, *Tetrahedron*, 1998, **54**, 3983–3998.
10 M. F. Gordeev, G. W. Luehr, H. C. Hui, E. M. Gordon and D. V. Patel, *Tetrahedron*, 1998, **54**, 15879–15890.
11 S. Hanessian and X. Fang, *Tetrahedron Lett.*, 1998, **39**, 733–736.
12 F. Stieber, R. Mazitschek, N. Soric, A. Giannis and H. Waldmann, submitted for publication.