ORGANIC LETTERS

2004
Vol. 6, No. 22
3921−3924

New Scavenger Resin for the Reversible Linking and Monoprotection of Functionalized Aromatic Aldehydes

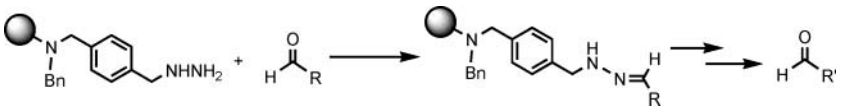
Mingzhao Zhu, Eelco Ruijter, and Ludger A. Wessjohann*

Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle (Saale), Germany

wessjohann@ipb-halle.de

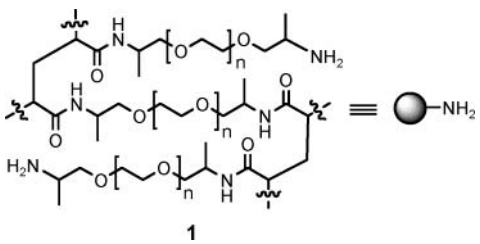
Received July 19, 2004

ABSTRACT



Polymer-supported benzylhydrazines were synthesized using poly(ethylene glycol) acrylamide (PEGA) resin. They can be used to scavenge electrophiles reactive with hydrazine. Especially aromatic aldehydes can be captured selectively, monoprotected, and reversibly linked in the presence of other functional groups, including electrophilic ones. Various reactions can be performed on these protectively linked aldehydes, which afterward can be released either with full restoration of the aldehyde function or, alternatively, with simultaneous conversion.

Linkers play a key role in solid-phase organic chemistry (SPOC).[1] A correctly chosen linker enables the successful and selective attachment of building blocks onto a chosen solid phase and convenient cleavage of the final products from the resin. Our laboratory is engaged in designing a novel polymer-linker system for macrocycle libraries of antibiotic and anticancer compounds such as rifamycins, epothilones, vancomycin mimics and their derivatives. The synthesis of macrocycles with structural diversification can be achieved by means of combinatorial chemistry.[2] Since some transformations in SPOC involve biocatalysts or polar metallic organic reagents, $PEGA_{1900}$ was used as the supporting resin (Figure 1).[3] Unlike other resins, $PEGA_{1900}$ is an unique hydrophilic support and enables reactions in aqueous or other highly polar solutions. Its spacer, consisting of 43 ethylene glycol units on average and a backbone of cross-linked methyl acrylamide, reduces the loading to 0.2 mmol/g but ensures that bound molecules are fully accessible to bulky enzymes or catalysts and polar reagents that previously failed in less polar polystyrene-based PEG-ylated resins.[3,4] Several solid-phase syntheses of oligosaccharides and peptides have been reported using $PEGA_{1900}$.[5] On-bead screening of bound substrates is also possible.[6]



1

Figure 1. $PEGA_{1900}$ ($n = 43$)

Due to the fact that most of our target macrocycles feature aldehyde functional groups, the linker for these compounds

(1) (a) Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*, 2nd ed.; Wiley-VCH: Weinheim, 2000; Chapter 3, pp 33−132. (b) Zaragoza Dörwald, F. *Organic Synthesis Highlights V;* Wiley-VCH: Weinheim, 2003; pp 251−264. (c) Bräse, S.; Dahmen, S. *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; VCH: Weinheim, 2002; Chapter 4, pp 59−169. (d) James, I. W. *Tetrahedron* **1999**, *55*, 4855−4946. (e) Gordon, K.; Balasubramanian, S. *J. Chem. Technol. Biotechnol*. **1999**, *74*, 835−851. (f) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091−2157. (g) Bräse, S.; Dahmen, S. *Chem. Eur. J.* **2000**, *6*, 1899−1905.

(2) (a) Wessjohann, L. A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W. *Mol. Diversity* **2005**, *9*(*1*), in print. (b) Wessjohann, L. A.; Ruijter, E. *Mol. Diversity* **2005**, *9*(*1*), in print. (c) Wessjohann, L. A.; Ruijter, E. Strategies for Total and Diversity-Oriented Synthesis of Natural Product(-Like) Macrocycles. In *Topics in Current Chemistry*; Mulzer, J. H., Ed.; Springer: Heidelberg, 2004; Vol. 243; p 137−184.

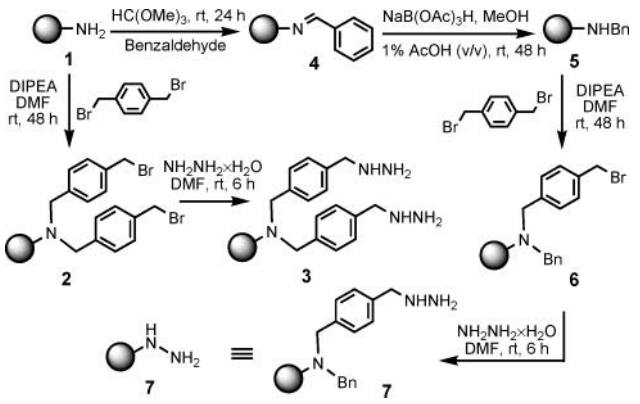
(3) In preceding studies with various commercial resins and linkers, including polystyrene-based sulfonylhydrazine resins, we were unsuccessful in performing enzymatic and organometallic reactions of resin-bound substrates in sufficient yield or quality. (Cf. our recent study of Cr(II)-mediated reactions with SPOC: Wessjohann, L. A.; Wild, H.; Schrekker, H. S. *Tetrahedron Lett.* **2004**, in print.)

10.1021/ol048610h CCC: $27.50
Published on Web 10/08/2004

should, ideally, be able to bind and release especially aldehydes readily. Usually, aldehydes are immobilized to linkers as acetals, enol ethers, or enamines.[7−9] These methods, however, have the drawbacks of either inconvenient attachment or cumbersome cleavage, apart from problems deriving from the presence of sensitive functional groups like, e.g., enol ethers or acetals, encountered in natural compounds such as rifamycin. In contrast to these, hydrazine-based linkers are promising alternatives.[10] Commercial tosylhydrazine resins are good scavengers but not ideal for modifications and release.[3] A few examples describing aldehydes as the cleavage products have been reported with polystyrene-based (Merrifield) resins.[11] Lazny recently reported new spacers.[11a,b] However, the synthetic route was complicated by a N−N bond formation.

We have found that benzylhydrazine linkers reversibly link aldehydes smoothly, allow modification reactions, and can be produced easily. We herewith present two novel scavenging linkers (**3** and **7**) anchored on PEGA polymer having hydrophilic core properties suitable for biocatalytic or large organometallic reagents (Scheme 1). Commercial $PEGA_{1900}$

Scheme 1



(**1**) was reacted with excess 1,4-di(bromomethyl)benzene to obtain the dialkylation product **2**. Treatment with hydrazine monohydrate converted **2** to linker **3** with doubled loading capacity. The increased loading is useful for scavenging reactions. For other applications, however, the bound substrates may be too close together. This is not favorable, especially for cyclizations under solid-phase pseudodilution conditions or when enzymatic access is required. For the reversible linking and synthetic modification of substrates, the monobenzylhydrazine linker **7** is preferred. To obtain this more suitable linker, **1** was reacted with benzaldehyde to give imine **4**. Trimethyl orthoformate was used as both solvent and dehydrating reagent for the imine formation.[12] After reduction of **4** to the secondary amine, the addition of 1,4-di(bromomethyl)benzene led to the monofunctionalized benzyl bromide **6**, which was readily substituted with hydrazine monohydrate to give the desired resin **7**.

The linking of various aldehydes to **7** by hydrazone bond formation is very straightforward. The main problem of hydrazone-linking lies in finding suitable cleavage condition to release the aldehydes unharmed to the solution phase. Several research groups reported the cleavage of aldehydes or ketones from hydrazone bonds.[11] For example, Lazny used 10% TFA in THF for ketone cleavage, but this condition is too harsh for aldehydes presenting additional sensitive functional groups as in complex natural products.[11a,b] Aldehydes and ketones can also be released from semicarbazone linkages in acid together with acetaldehyde or formaldehyde.[11c,d] However, the cleavage products in these cases were always seriously contaminated by side products from formaldehyde or acetaldehyde.[13] Some but not all of the side products can be washed out with water, but this cleavage is still impractical in combinatorial synthesis.

Although all these methods worked for our system too, we soon noted that using acetone instead of formaldehyde or acetaldehyde could circumvent the problems.[14,15] THF was

(4) (a) Meldal, M. *Tetrahedron Lett.* **1992**, *33*, 3077−3080. (b) Rademann, J.; Grotli, M.; Meldal, M.; Bock, K. *J. Am. Chem. Soc.* **1999**, *121*, 5459−5466. (c) Basso, A.; Ebert, C.; Gardossi, L.; Linda, P.; Tran Phuong, T.; Zhu, M.; Wessjohann, L. *Chem. Commun.* **2004**, submitted. (d) Basso, A.; De Martin, L.; Gardossi, L.; Margetts, G.; Brazendale, I.; Bosma, A. Y.; Ulijn, R. V.; Flitsch, S. L. *Chem. Commun.* **2003**, 1296−1297. (e) Doeze, R. H. P.; Maltman, B. A.; Egan, C. L.; Ulijn, R. V.; Flitsch, S. L. *Angew. Chem.* **2004**, *116*, 3200−3203; *Angew. Chem. Int. Ed.* **2004**, *43*, 3138−3141.

(5) Some recent examples: (a) Barkley, A.; Arya, P. *Chem. Eur. J.* **2001**, *7*, 555−563. (b) Wu, C. W.; Sanborn, T. J.; Zuckermann, R. N.; Barron, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 2958−2963. (c) Melnyk, O.; Fruchart, J.-S.; Grandjean, C.; Gras-Masse, H. *J. Org. Chem.* **2001**, *66*, 4153−4160. (d) Kohli, R. M.; Walsh, C. T.; Burkart, M. D. *Nature* **2002**, *418*, 658−661. (e) Pastor, J. J.; Fernández, I.; Rabanal, F.; Giralt, E. *Org. Lett.* **2002**, *4*, 3831−3833. (f) Ulijn, R. V.; Baragana, B.; Halling, P. J.; Flitsch, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 10988−10989.

(6) St. Hilaire, P. M.; Meldal, M. *Angew. Chem.* **2000**, *112*, 1210−1228; *Angew. Chem. Int. Ed.* **2000**, *39*, 1162−1179.

(7) Selected examples for acetal linkers: (a) Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Bakker, W. I.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4179−4182. (b) Metz, W. A.; Jones, W. D.; Ciske, F. L.; Peet, N. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2399−2402. (c) Ede, N. J.; Bray, A. M. *Tetrahedron Lett.* **1997**, *38*, 7119−7122. (d) Bertini, V.; Lucchesini, F.; Pocci, M.; De Munno, A. *Tetrahedron Lett.* **1998**, *39*, 9263−9266. (e) Wong, J. Y.; Leznoff, C. C. *Can. J. Chem.* **1973**, *51*, 3756−3764.

(8) Selected examples for enol ether linkers: (a) Fraley, M. E.; Rubino, R. S. *Tetrahedron Lett.* **1997**, *38*, 3365−3368. (b) Ball, C. P.; Barrett, A. G. M.; Commercon, A.; Compère, D.; Kuhn, C.; Roberts, R. S.; Smith, M. L.; Venier, O. *J. Chem. Soc., Chem. Commun.* **1998**, 2019−2020.

(9) Selected examples for enamine linkers: (a) Hird, N. W.; Irie, K.; Nagai, K. *Tetrahedron Lett.* **1997**, *38*, 711−7114. (b) Crawshaw, M.; Hird, N. W.; Irie, K.; Nagai, K. *Tetrahedron Lett.* **1997**, *38*, 7115−7118.

(10) (a) Stieber, F.; Grether, U.; Waldmann, H. *Chem. Eur. J.* **2003**, *9*, 2370−2381. (b) Kirchhoff, J. H.; Bräse, S.; Enders, D. *J. Comb. Chem.* **2001**, *3*, 71−77.

(11) (a) Lazny, R.; Nodzeweska, A.; Wolosewicz, K. *Synthesis* **2003**, 2858−2864. (b) Lazny R.; Michalak, M. *Synlett* **2002**, 1931−1934. (c) Lee, A.; Huang, L.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 9907−9914. (d) Murphy, A. M.; Dagnino, R., Jr.; Vallar, P. L.; Trippe, A. J.; Sherman, S. L.; Lumpkin, R. H.; Tamura, S. Y.; Webb, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 3156−3157.

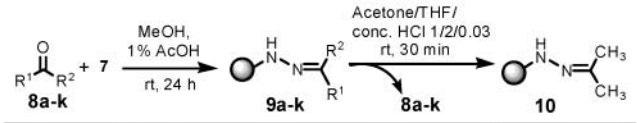
(12) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937−2940.

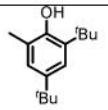
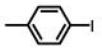
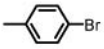
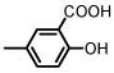
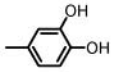
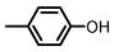
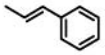
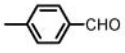
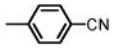
(13) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356−1361.

(14) Similar hydrazone exchange reaction was described by Buchwald for precursors of a Fischer indole synthesis: Wagaw, S.; Yang, B. H.; Buchwald, S. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263.

(15) Acetone proved to be most useful. It is the cheapest ketone of sufficient reactivity for the hydrazone exchange, excess is easily removed from the product, and the resulting resin with acetone capping is still reactive enough to allow recovery of the free solid-phase hydrazine by hydrazine exchange if desired. Unlike with aldehydes, we saw much less (**8h**,**i**) or mostly no unwanted reactivity and much higher enzyme compatability. Only **8j** is reactive in either scavenge or cleavage.

Table 1.



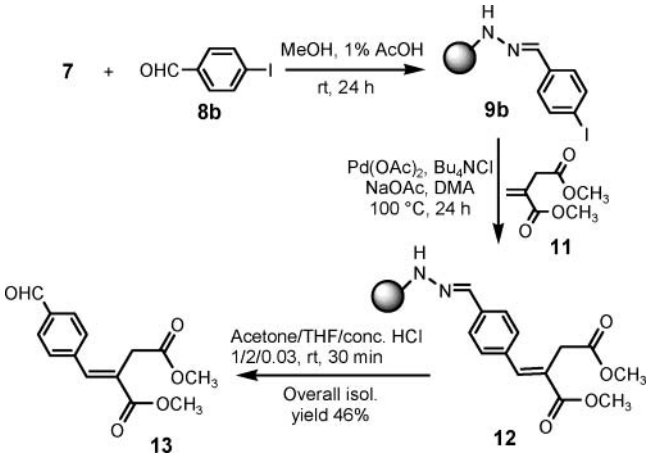
entry	substrates	R^1	R^2	purity (%)	yield[a] (%)
1	**8a**		H	87	83
2	**8b**		H	80	72
3	**8c**		H	99	84
4	**8d**		H	97	55
5	**8e**		H	61	45
6	**8f**		H	99	45
7	**8g**		H	95	43
8	**8h**		H	37	65
9	**8i**		H	85	<10
10	**8j**		H	-	0
11	**8k**			-	<10

[a] Combined yield for both steps with standard conditions (not optimized).

used as the cosolvent to increase the swelling. To prove this finding, we tested aldehydes **8a**−**j** and benzophenone **8k** on resin **7** (Table 1). Linking them in MeOH with 1% acetic acid (v/v) gave the resin-bound products **9a**−**k**. For cleavage, these were treated with THF−acetone−HCl. Acetone exchanged with **9** to drive the reaction to completion, and satisfactory results were achieved. Most aldehydes were recovered in high to moderate yields but were often excellent with respect to purity. The reason for the low recovery yield of benzophenone (**8k**) certainly is a combination of the higher stability of the hydrazone and especially its steric hindrance, which is not overcome by the mild cleavage condition. In addition to this scavenge and traceless release of aldehydes, captured aldehydes can be exposed to intermittent reactions.

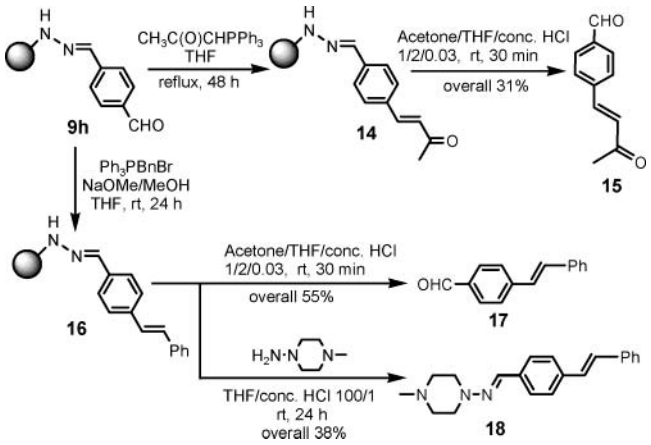
As an example, a Heck coupling was performed with polymer-protected substrate **8b** (Scheme 2). The bound aldehyde **9b** reacted with dimethyl itaconate (**11**) to give the coupling product **12**.[16] By using the established cleavage method, the final coupling product **13** was obtained in 46% overall isolated yield.

Scheme 2



Usually, it is difficult to sequentially address the two aldehyde groups of **8h** selectively in solution-phase reactions. This goal can be achieved under solid-phase conditions, taking advantage of the pseudodilution effect of matrix separation and selective monoprotection.[5e] For a demonstration, two Wittig reactions were carried out after **8h** was bound to **7** (Scheme 3). Thus, the resulting **9h** was converted

Scheme 3



to **14** by treatment with acetylmethylene triphenylphosphorane, and product **15** was obtained after cleavage. Analogously, benzyltriphenylphosphonium bromide transformed **9h** to **16**. At this stage two cleavage methods were applied: (1) The established THF−acetone−HCl condition released aldehyde **17** in 55% overall yield. (2) A second hydrazine, 1-amino-4-methylpiperazine, can attack **16** to give **18** in a transimination reaction, with a newly formed hydrazone bond and the recovered resin **7**. It should be noted here that these reactions were by no means optimized to solid-phase conditions, and thus yields are not representative.

(16) Bertina, S.; Wendeborn, S.; Brill, W. K. D.; De Mesmaeker, A. *Synlett* **1998**, 676−678.

So far we have examined the suitability of small aromatic molecules on resin **7**. Because our future interest will be focused on SPOC of highly complex macrocyclic (aromatic) aldehydes and ketones, we chose 3-formyl rifamycin (**19**),[17] a derivative of rifamycin SV[18] and a typical macrocyclic aldehyde, to explore the (optimization) potential of the linkage−cleavage methods (Figure 2). 3-Formyl rifamycin

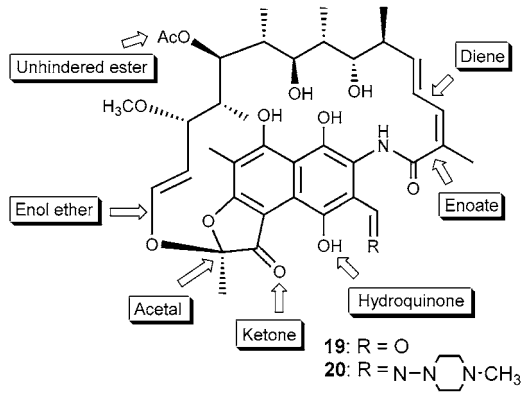
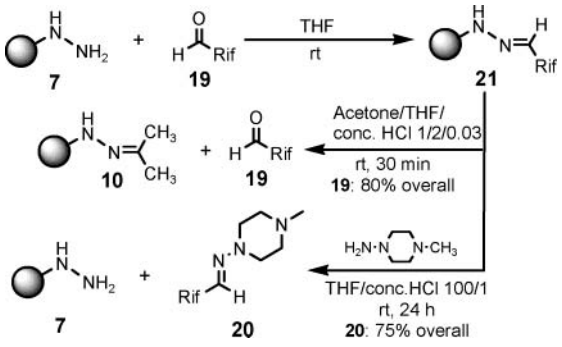


Figure 2. 3-Formyl rifamycin SV (**19**), rifampicin (**20**), and the main functional groups.

is a compound with several sensitive functional groups such as ketone, acetate, enol ether, and dienoate, which can be reactive to hydrazines as well as acidic hydrolysis. Its red color allows us to follow linkage and cleavage steps easily.

The attachment of **19** onto **7** was carried out in neutral THF to give **21** (Scheme 4). After only a small degree of optimization of reaction time and temperature, the acidic release gave 80% overall yield, including scavenging. This

Scheme 4



surprisingly high yield shows that resin **7**, together with the linkage−cleavage methodology and substrate-adapted conditions, has the potential to be applied in further reactions of different complicated aromatic aldehydes on solid phase.

For the medicinal use, hydrazones of the rifamycin family are more important, especially the trade drug rifampicin (**20**), a hydrazone derivative of **19** (Figure 2).[13,19] We achieved its synthesis starting from resin-bound 3-formyl rifamycin **21**. 1-Amino-4-methylpiperazine exchanged with **21** to release rifampicin **20** to solution in 75% yield, leaving behind the reusable polymer **7** (Scheme 4).

In summary, we have developed a new type of benzylhydrazine-based linker−resin combination suitable for different aldehydes and reactions requiring a polar environment or excessive swelling. It can be used as a scavenger resin to selectively remove excess aldehyde (or, if applied for a longer time or at higher temperature, other hydrazine reactive groups) from solution-phase reactions. More useful is the selective scavenging of (aromatic) aldehydes that then can be selectively recovered. Intermittently, these aldehydes may be subjected to chemical modification. In case of dialdehydes, monoprotection is effective. As examples, one Heck coupling and two Wittig reactions were tested to modify the aldehydes on solid phase. The cleavage reagents can be either acetone or hydrazines to release aldehyde or hydrazones, respectively. Both of the cleavage conditions are mild enough to allow the release of the multifunctional macrocycles **19** and **20** in high yields. Other cleavage conditions such as acidic hydrolysis, methanolysis, or aldehyde exchange are possible, sometimes even faster, but may cause more side reactions. A new route to combinatorial libraries of aldehydes, or, e.g., rifamycin derivatives, can be established with this (traceless) linker and the straightforward scavenge−release methodology.

Acknowledgment. This work was supported by an EU grant as part of the Combiocat Project. We thank Polymer Labs for $PEGA_{1900}$ resin.

Supporting Information Available: Experimental procedures for the synthesis and attachment to resins and characterization data for compounds **13**, **15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048610H

(17) (a) Maggi, N.; Arioli, V.; Sensi, P. *J. Med. Chem.* **1965**, *8*, 790−793. (b) Maggi, N.; Gallo, G. G.; Sensi, P. *Farmaco Ed. Sci.* **1967**, *22*, 316−325.

(18) Vavricka, S. R.; van Montfoort, J.; Ha, H. R.; Meier, P. J.; Fattinger, K. *Hepatology* **2002**, *36*, 164−172 and references cited therein.

(19) (a) Füresz, S.; Arioli, V.; Pallanza, R. *Antimicrob. Agents Chemother.* **1965**, 770−777. (b) Gallo, G. G.; Radaelli, P. *Anal. Profiles Drug Subs.* **1976**, *5*, 467−513.