2-Oxopiperazine Scaffolds by [3+2] Cycloaddition Reactions with a Polymer-Supported Cyclic Nitrone

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Dedicated to Professor Helmut Schwarz on the occasion of his 60th birthday

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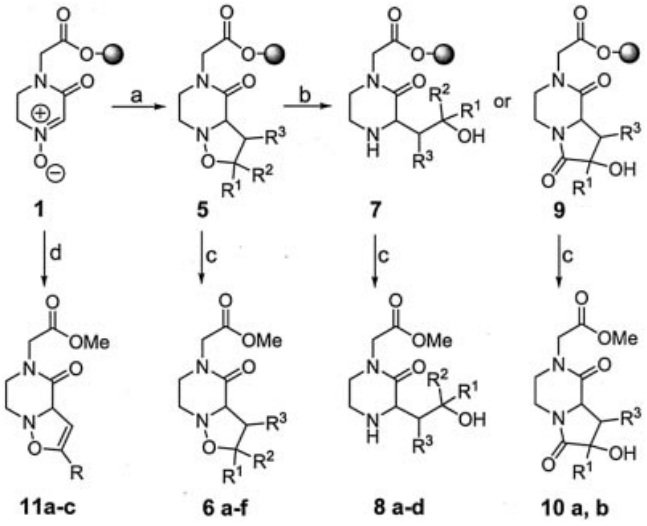
Isoxazolidines and 1,3-aminoalcohols with a piperazin-2-one skeleton were readily prepared on a solid support through [3+2] cycloaddition and subsequent N–O-bond cleavage, starting from a polymer-supported cyclic nitrone. Libraries of functionalized 1,3-aminoalcohols and their derivatives were obtained by automated amine acylation and Mitsunobu reactions on a solid support. The key to success is the oxidation of the immobilized cyclic secondary amine precursor to the nitrone on a solid support and the reductive N–O-bond cleavage of the isoxazolidines, employing $Mo(CO)_6$.

Introduction

Among the target molecules for synthesizing libraries on solid supports, heterocycles remain of interest in lead-finding processes for medicinal, as well as agricultural chemistry. In heterocyclic chemistry, 1,3-dipolar cycloaddition reactions are among the most versatile and important reactions for the construction of five-membered ring systems.[1,2] For reactions of nitrones on a solid support, either the alkenes and alkynes or the nitrones have to be immobilized. So far, polymer-bound alkenes[3,4] have been investigated and only acyclic nitrones have been generated on solid supports,[5] through immobilization of *N*-substituted hydroxylamines and commercially available aldehydes.

Cyclic nitrones are generally prepared in solution from secondary amines by oxidation.[6,7] We herein report the synthesis and application of the polymer-bound cyclic nitrone **1** (see Scheme 1) starting from the parent secondary amine on a Wang resin (p-benzyloxybenzylalcohol resin). This approach opens up an access to 2-oxopiperazine derivatives, which are amongst the most privileged biologically active scaffolds.[8] Furthermore, resulting isoxazolidines and isoxazolines are well suited for functionalization. The N−O bond of isoxazolidines is amenable to reductive[9,10] and oxidative[11] N−O-bond cleavage, furnishing functional groups for subsequent transformations. In this paper, we report on the development of [3+2] cycloadditions of the polymer-bound nitrone **1** with alkenes and alkynes furnishing isoxazolidines **6** (Scheme 1, Table 1) or isoxazolines **11**, after cleavage from the resin. Starting from the polymer-supported isoxazolidines **5**, methods for reductive as well as oxidative N−O-bond cleavage were investigated. Subsequent transformations of polymer-bound 1,3-aminoalcohols **7** and lactams **9** to produce libraries by amine acylation and Mitsunobu reactions, employing automated synthesis, are also described.



Scheme 1. 2-Oxopiperazine scaffolds by [3+2] cycloaddition reactions with a polymer-bound cyclic nitrone; reagents and conditions: a) alkene, THF, 65 °C; b) $Mo(CO)_6$, MeCN/water (15:1), 85 °C (**5** → **7** or **5** → **9** for R^2 = COOMe); c) NaOMe, MeOH/THF (1:4), r.t.; d) alkyne, THF, 60 °C, 1−2 h; then NaOMe, MeOH/THF

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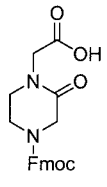
Table 1. Synthesis of the cycloadducts **6**, the 1,3-aminoalcohols **8** and the lactams **10** (see Scheme 1) on a solid support and comparison of the N−O-bond cleavage on a solid support with solution-phase studies

Entry	Cyclo-adduct **6**	R^1	R^2	R^3	Purity **6** (%)[a]	Yield **6** (%)[b]	Product **8** or **10**	Yield **8** or **10** (%)[c]	Overall yield, SPOS (%)[b,c] **8** or **10**	Overall yield, solution (%)[d] **8** or **10**
1	**6a**	H	$CH_2OC_6H_5$	H	85	40	**8a**	35	20	6
2	**6b**	R^2	C_5H_{10}	H	90	82	**8b**	51[e]	29	−[f]
3	**6c**	H	R^3	(C=O)NMe(C=O)	92	28	**8c**	25	15	9
4	**6d**	H	R^3	(C=O)NPh(C=O)	−	−	**8d**	13	8	11
5	**6e**	H	CO_2Me	H	95	27	**10a**	66	38	20
6	**6f**	Me	CO_2Me	H	90	37	**10b**	31	18	not tested

[a] Purity determined by analytical RP-HPLC at 210 nm. [b] Isolated yields after purification by preparative RP-HPLC. [c] See reference.[15] [d] See reference.[17] [e] Crude product yield. [f] Not calculated: isolated yield of 1,3-aminoalcohol > 100 %, because of $Mo(CO)_6$ impurities.

Results and Discussion

The polymer-bound nitrone **1** was synthesized from the carboxylic acid **2** in a four-step sequence.[12,13] Immobilization of compound **2** on a Wang resin (substitution value: 0.4 mmol/g up to 0.9 mmol/g) by treatment with DCC/DMAP in the presence of pyridine (twice), was followed by capping with Ac_2O/pyridine (1:3).[14,15] For removal of the Fmoc protecting group, 50 % morpholine/DMF was applied. The secondary amine **3** was oxidized with 30 % aqueous H_2O_2 (4.4 equiv.) using $Na_2WO_4 \times 2\ H_2O$ as a catalyst in methanol/THF (1:1) at room temperature to afford nitrone **1**, with a distinctive IR absorption at 1563 cm^{-1}.[6] Oxidation with the Davis reagent (2-benzsulfonyl-3-phenyloxaziridine)[7,16] (4.4 equiv.) in chloroform yielded comparable results. For model studies in solution, nitrone **4** was synthesized.[17]



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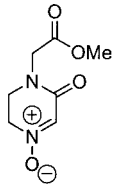

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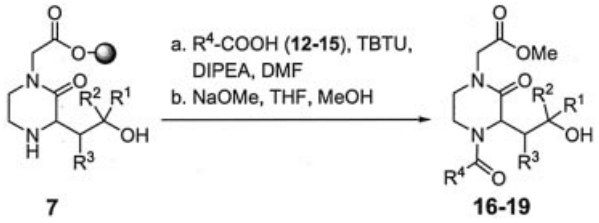
Thermal 1,3-dipolar cycloaddition reactions with alkenes yielding polymer-bound isoxazolidines **5** (Scheme 1) were successfully carried out manually in THF at 65 °C.[18,19] Complete turnover was generally observed by using 16−17 equiv. of the alkene in a 1−3 h reaction time as determined by IR monitoring. Methylenecyclohexane as dipolarophile (Table 1, entry 2) reacted completely only after 8 h when applied in large excess (59 equiv.) to afford the polymer-supported isoxazolidine **5b**. Acid-catalyzed cleavage procedures applying TFA and a variety of scavengers failed. Among the base-catalyzed cleavage protocols investigated (1 M NaOH in isopropanol/THF; nBu_4NOH in THF; KCN, Et_3N in MeOH/benzene), the application of NaOMe in MeOH/THF (1:4) at room temperature proved to be a straightforward procedure for the cleavage and isolation of isoxazolidines **6** (Scheme 1, Table 1) with a piperazin-2-one skeleton.[19] All but the isolation of cycloadduct **6d**, derived from *N*-Phenyl maleic imide, were successful. The isoxazolidines were obtained with complete regioselectivity and in > 85% purity after cleavage from the resin. The products were isolated in 28−82 % yield after purification by preparative RP-HPLC (six-step sequence on solid support: 81−97 % calculated yield per step).

Reductive N−O-bond cleavage of the polymer-bound isoxazolidines **5** was investigated next, by using $Mo(CO)_6$ (5 equiv. up to 14 equiv.) in wet acetonitrile at 85 °C (5−29 h), which yielded the aminoalcohols **8** or the lactams **10** in 50−99 % purity after cleavage from the resin and in 13−66 % isolated yield after preparative RP-HPLC. The lactams **10a** and **10b** were obtained from the polymer-bound methyl acrylate- and methyl methacrylate-derived cycloadducts [**5e** (R^2 = COOMe) → **9a** → **10a**; **5f** (R^2 = COOMe) → **9b** → **10b**] formed by intramolecular amide formation.[20] The products isolated after the seven-step sequence on solid support were generally of higher purity and in higher yields than those of the solution-phase studies. The overall yields of the 1,3-aminoalcohols **8** and the lactams **10** (see Table 1), calculated from the reactions on solid supports, including the preparation of the precursor molecules in solution (twelve-step[15] sequence), are higher than the calculated overall yields for solution-phase studies (seven-step[17] sequence). These results prove quite impressively the advantages of the syntheses on solid supports, in the light of the laborious workup and purification procedures in solution-phase studies.

5-Substituted isoxazolines **11** were obtained (Scheme 1) by using monosubstituted alkynes in thermal 1,3-dipolar cycloaddition reactions with the polymer-bound nitrone **1**.[21] The reaction of 4-bromophenylacetylene yielded solely regioisomers, presumably for steric reasons, in approximately 53:47 ratio (^1H NMR spectroscopy) and the expected 5-substituted cycloadduct **11b** was preferentially formed. Starting from phenylacetylene, the final cycloadduct **11a** was obtained in 90 % purity after cleavage from the resin and isolated in 54 % yield by preparative RP-HPLC. A large excess of the alkynes (≥ 17 equiv.) and shorter reaction times (1−2 h instead of 5−21 h in solution-phase studies) resulted in efficient and complete conversion on a solid support. There was no evidence of thermal re-

arrangement or of decomposition reactions of isoxazolines, as has been observed in solution-phase studies.

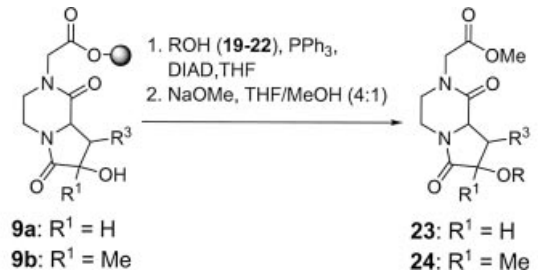
With the polymer-bound 1,3-aminoalcohols **7** and the lactams **9**, transformations of the hydroxy and amino functionalities were studied next by automated solid-phase synthesis. No manual exploratory experiments to define optimal reaction conditions were carried out. For amine acylation of the building blocks **7a**, **7b**, **7c** and **7d**, the four carboxylic acids **12**−**15** [**12**: $CH_3CH(CH_3)CH_2CH_2CO_2H$; **13**: 3-$MeC_6H_4CH_2CO_2H$; **14**: 6-$ClC_5H_3N$-3-$CO_2H$; **15**: 3-$FC_6H_4CO_2H$] were tested applying TBTU, DIPEA in DMF at room temperature under standard conditions (Scheme 2).



Scheme 2. Library of piperazin-2-ones, derived from the polymer-supported 1,3-aminoalcohols **7** by automated amine acylation

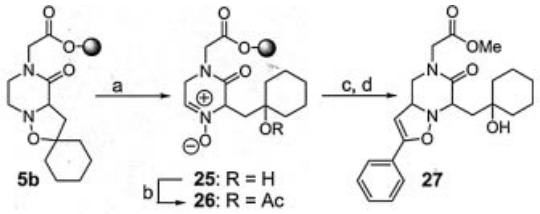
Only the polymer-bound 1,3-aminoalcohol **7d**, derived from *N*-phenyl maleic imide, proved to be a poor substrate. All the products obtained after cleavage from the resins were analyzed by RP-HPLC and LC-MS.[22] Esters **16**−**18** were obtained in 3−11 % isolated yield by preparative RP-HPLC and were fully characterized (eight-step sequence on solid-support: 65−76 % calculated yield per step).

Standard Mitsunobu-reaction conditions were chosen for the modification of the hydroxyl group of the building blocks **9a** and **9b** (see Scheme 3) with four substituted phenols [**19**: 4-Cl,3-Me-C_6H_3-OH, **20**: 3-F-C_6H_4-OH, **21**: 3-F_3C−C_6H_4-OH, **22**: 3-(H_3C−C=O)-C_6H_4-OH]. Building block **9a** reacted readily and completely, furnishing **23a**−**d** and the parent acids in > 96 % purity (RP-HPLC/LC-MS) after cleavage (NaOMe in methanol/THF 1:4) from the resin. However, **9b** did not react with suitable efficiency (10−20 % purity) presumably for steric reasons, as the Mitsunobu reaction hardly proceeds for tertiary amines (**23**, **24**: 5−20 % isolated yield after preparative RP-HPLC; nine-step sequence on solid support: 72−84 % calculated yield per step).



Scheme 3. Automated Mitsunobu reactions of polymer-bound isoxazolidine-derived lactams **9a** and **9b**

Finally, starting from the building block **5b** ($R^1 = R^2 = C_5H_{10}$, R^3 = H) oxidative N−O-bond cleavage, applying MCPBA[11] and furnishing the polymer-bound second-generation aldonitrone **25** was investigated manually (see Scheme 4). After acylation, which yielded **26**, the subsequent [3+2] cycloaddition with phenylacetylene gave isoxazoline **27**, isolated in 9 % yield by RP-HPLC, after cleavage from the resin (ten-step reaction sequence).



Scheme 4. Oxidative N−O-bond cleavage on solid support; reagents and conditions: a) MCPBA, DCM, −78 °C, 20 min; b) Ac_2O/pyridine (1:3), r.t.; c) phenylacetylene/THF (1:1), 60 °C, 1 h; d) NaOMe, MeOH/THF (1:4), r.t., 23 h (9 %)

Exploratory experiments in solution and on solid supports indicated the need for acetylation of the hydroxyl group, since second-generation nitrones are prone to intramolecular addition of the alcohol functionality to the nitrone double bond, furnishing a bicyclic hydroxylamine, which is stable under the conditions of thermal [3+2] cycloaddition reactions.

Conclusion

In summary, we have demonstrated how piperazin-2-one scaffolds can be built on a solid support through [3+2] cycloaddition reactions and by subsequent reductive N−O-bond cleavage or oxidative N−O-bond cleavage of isoxazolidines derived from alkenes. Polymer-bound 1,3-aminoalcohols and lactams with a piperazin-2-one skeleton are found to be readily available by employing $Mo(CO)_6$ for reductive N−O-bond cleavage and have been applied as useful building blocks for further transformations on solid supports, e.g. amine acylations or Mitsunobu reactions.

Acknowledgments

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[14] All reactions on solid support were monitored by IR spectroscopy. The resin attachment was determined by the disappearance of the distinct IR absorption of the Wang resin at about 3576 cm^{-1}. All resins prepared were characterized after attachment of the Fmoc-protected nitrone precursor by elemental analysis (nitrogen analysis: > 95 % conversion).

[15] Solid phase studies: the 1,3-dipolar cycloadditions and N−O-bond cleavages on solid support were carried out manually on a 0.1 mmol scale up to a 1.3 mmol scale. For all reactions, overall yields were calculated including the synthesis of the piperazin-2-one precursor **2**, which is commercially available since July 2003.

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[17] Solution phase studies: the synthesis and application of nitrone **4** (five-step sequence: 43 % overall yield) will be described elsewhere. All overall yields for solution-phase studies were calculated by including the synthesis of nitrone **4**. For the application of a 3-benzyl-2-oxopiperazine-derived nitrone, see reference[12].

[18] The 1,3-dipolar cycloaddition reactions of alkenes were studied in detail in solution (ten examples) and on a solid support (twelve examples) with monosubstituted alkenes (allylphenylether, allylcyclohexylamine, 2-vinylpyridine, 4-vinylpyridine, *N*-methyl-*N*-vinyl-acetamide, acrylic acid methyl ester, *N*,*N*-dimethyl acrylic acid amide), 1,1-disubstituted alkenes (methylencyclohexane, methacrylic acid methyl ester) and 1,2-disubstituted alkenes (*N*-methyl maleic imide, *N*-phenyl maleic imide, 5*H*-furan-2-one). Reactions carried out with allylcyclohexylamine, *N*-methyl-*N*-vinyl acetamide, *N*,*N*-dimethyl acrylamide and 5*H*-furan-one on solid support gave inconsistent and unsatisfactory results in our hands or failed. The regioselectivities observed were in accordance with solution phase chemistry, yielding 5-substituted isoxazolidines starting from monosubstituted and 1,1-disubstituted alkenes and 4-substituted isoxazolidines in cycloaddition reactions to 1,2-disubstituted alkenes.

[19] The structures of all non-polymeric compounds prepared by manual synthesis on solid support have been characterized by NMR-, IR- and elemental analysis or HRMS after purification of the crude products isolated by preparative RP-HPLC. The *endo*/*exo* selectivities of **6e** (ratio *endo*:*exo* = 57:43) and **6f** (ratio *endo:exo* = 100:0) were confirmed by NOE experiments.

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[21] **11a**: R = C_6H_5: 90 % purity, 54 % yield; **11b**: R = 4-Br-C_6H_4: 95 % purity, 23 % yield, **11c**: R = CH_2NMe_2: 90 % purity, 44 % yield.

[22] All crude products obtained by automated syntheses were characterized with RP-HPLC/LC-MS after cleavage from the resin. Percent conversions and purities were determined by analytical RP-HPLC at 210 nm based on the sum of the peak areas of the starting materials and all isomeric products observed for the desired esters and the parent acids.

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