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A new versatile linker for the solid-phase synthesis of secondary amines

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Abstract—A novel linker for the solid-phase synthesis of secondary amines based on an intramolecular cyclization was developed. The linker allows for a stepwise built-up of the secondary amines on the support. The feasibility was demonstrated in the parallel synthesis of a small set of different secondary amines.

Solid-phase synthesis has gained widespread acceptance in combinatorial chemistry related to drug discovery in order to accelerate lead generation and lead optimization.[1] Synthesis on a solid support shows a number of advantages as compared to solution chemistry. The most salient one is the possibility to apply excesses of reagents and removing them without involving time-consuming separation techniques. A prerequisite to widen the scope of reactions on solid support is the continuous development of suitable linker molecules with the desired properties.

An interesting class of molecules in drug discovery are amines. Secondary amines represent especially potent pharmacophores and are thus present in numerous biologically active compounds.[2] Furthermore, amines are often useful intermediates in synthetic organic chemistry.[3] An overview on different synthetic strategies for their preparation was published recently.[4] Up to now a number of linker systems for the solid-phase synthesis of secondary amines have been reported.

They are mainly based on well known protecting groups for amino functions (BOC and Z),[5,6] which were adapted to their application in solid-phase synthesis. Alternatively, the Rink-amide linker was employed, as demonstrated for the synthesis of pharmacologically interesting arylethanolamines.[7] However, all described protocols suffer from the limitation that the amines were attached as such to the solid-phase and were cleaved again after chemical modifications.[8,9] Herein, we describe a new method which allows for the de novo synthesis of secondary amines on the solid support.

In this approach the release of the secondary amines from the solid support proceeds via intramolecular cyclization. The basis for this work was led by a paper published by Fichert and Massing.[10] The adaptation of their strategy to solid support offers the possibility of a straightforward parallelization and guarantees a high level of purity of released secondary amines.

As solid support material we selected aminomethyl-polystyrene. However, before performing the reaction steps on solid support, the whole reaction sequence was evaluated in solution according to Scheme 1. Benzylamine was used as substitute for the aminomethyl-resin.

In contrast to Massing's route, commercially available trimellitic anhydride **1** was used which bears an additional carboxyl function for the later attachment to solid support. This was converted to the corresponding imide in a melting reaction using ammoniumcarbonate at 280°C in a yield of 80%.[11] The protection of the imide using tritylchloride and Hünig's base in CH_3CN under reflux furnished **2** in a modest yield (40%), probably due to sterical hindrance. Coupling to benzylamine and subsequent removal of the trityl protecting group with TFA in the presence of Et_3SiH as scavenger yielded **3** in 91%. The introduction of the first residue proceeded via a Mitsunobu reaction in a yield of 83%. Ring opening following a $NaBH_4$-reduction gave rise to two regioisomers with a total yield of 93% for both

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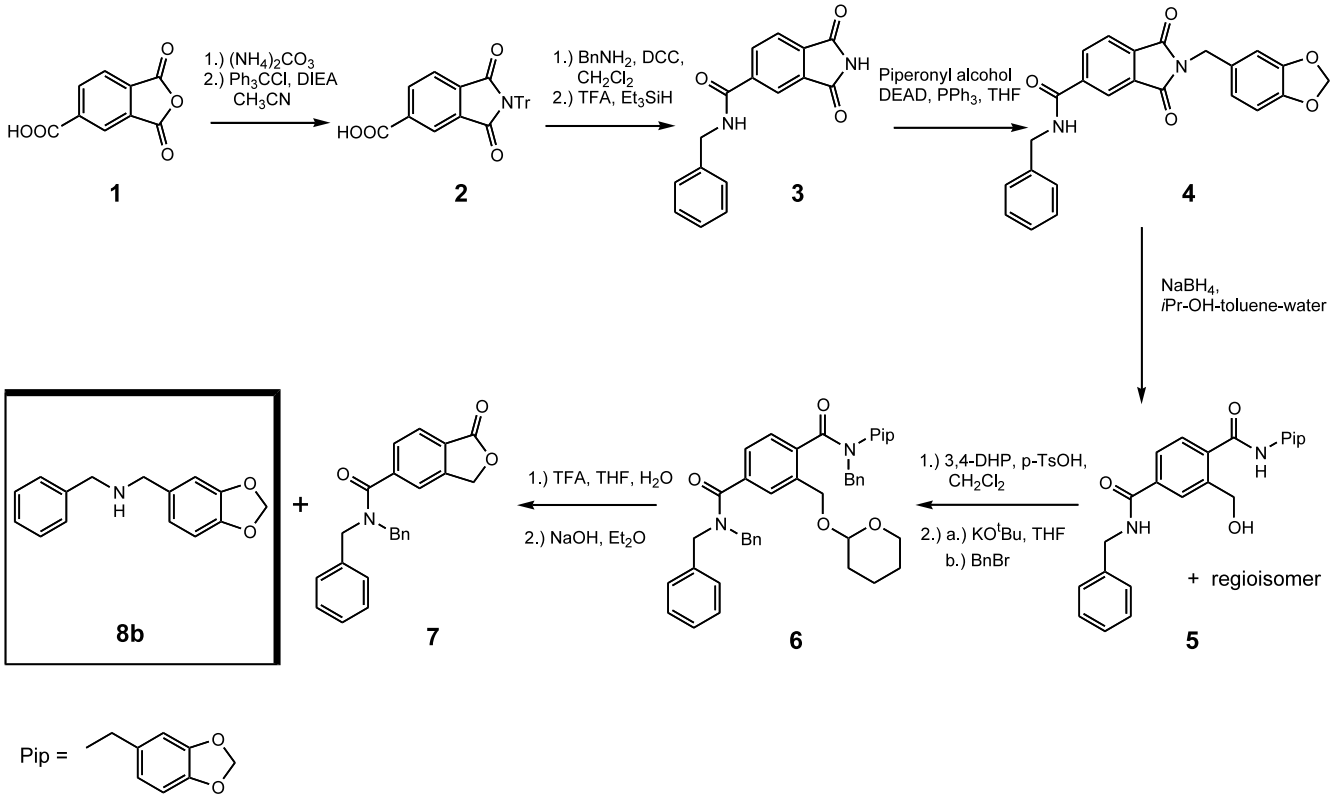
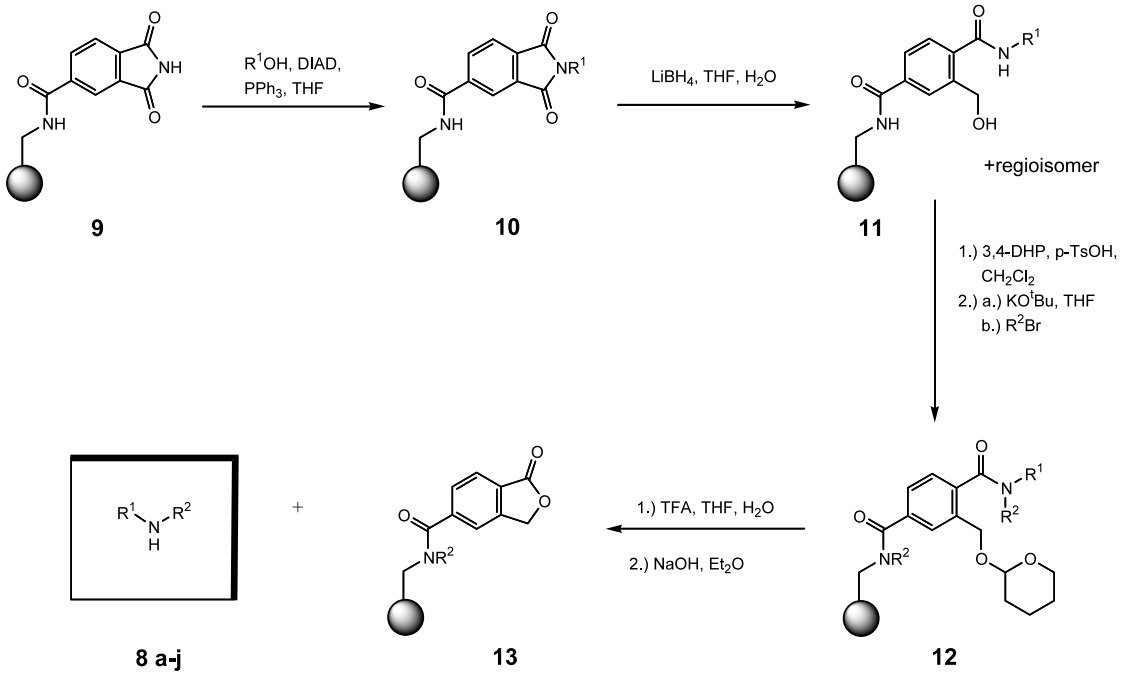
isomers. The synthesis was continued with purified isomer **5**. The hydroxyl function was protected as 3,4-dihydropyranyl ether with catalytic amounts of *p*-toluene sulfonic acid. The tetrahydropyranylether protection was chosen because of its stability towards the basic conditions of the ensuing alkylation step employed for the introduction of the second residue. After the alkylation with KO^{t}Bu in THF **6** was obtained in 80% yield. Finally, after cleavage of the THP-protecting-group, the amine was released as ammonium salt.

Instead of the THP-group alternative protecting groups can be employed and can be adapted to the chemistry



Scheme 1.



Scheme 2.

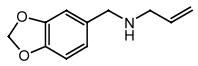
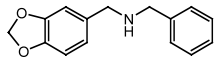
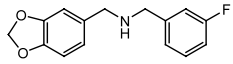
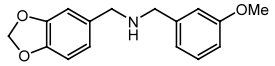
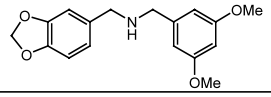
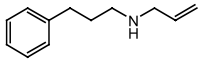
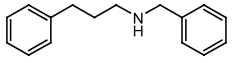
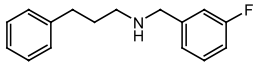
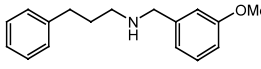
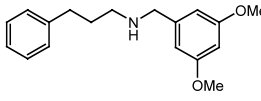
for further synthetic modifications of the desired secondary amines.

After the successful feasibility study, the approach was adapted to the synthesis on solid support. At the same time the synthesis of a small library of secondary amines was envisaged. The reactions on the solid-phase material were monitored by FT-IR spectroscopy. The actual synthetic route is outlined in Scheme 2.

Aminomethyl-functionalized polystyrene resin (loading: 0.85 mmol/g, 1% cross-linked) was used as support material. After each reaction step the resin was rinsed three times with DMF–water (50:50), DMF, CH_2Cl_2 and Et_2O. For some conversions the reaction conditions of solution chemistry had to be modified. The attachment of the linker molecule to the solid support was performed using TBTU[12] and Hünig's base in CH_2Cl_2. The completeness of the coupling reaction was verified by a Kaiser test.[13,14] The removal of the trityl group had to be performed with a mixture of TFA/CH_2Cl_2 (50/50 v/v) to guarantee a sufficient swelling of the resin and consequently a good accessibility of the reactive sites. Triethylsilane was added as scavenger. The NH bond of the unprotected imide-resin **9** showed a strong band at 3190 cm^{-1} for the imide-NH and one at 3333 cm^{-1} for the amide-NH. After alkylation of the imide-NH via Mitsunobu reaction resin **10** disclosed a single band at 3333 cm^{-1}, whereas the imide NH-band at 3190 cm^{-1} had disappeared. The subsequent reduction step was performed with $LiBH_4$ instead of $NaBH_4$ and the solvent mixture was changed to THF/water 20:1 because of the better swelling properties compared with the isopropanol–toluene–water mixture applied in the synthesis in solution. Water was added since the evaluation in solution manifested faster reduction rates in the presence of water. Resin **11** showed a characteristic broad absorption band between 3100 and 3600 cm^{-1} for the hydroxyl-function, whereas the C=O band at 1773 cm^{-1} had vanished. The introduction of the protecting group was performed at 0°C in CH_2Cl_2 and the ensuing alkylation procedure was modified in that way that KO^{t}Bu was removed with a syringe after an hour before a solution of the alkylating agent in THF was added. Reaction overnight yielded **12** and FT-IR revealed, that the NH-band and the OH-band had totally disappeared. The removal of the protecting group and subsequent cyclization were performed in a one-pot procedure in a mixture of TFA/THF/water (4/2/1) at 60°C for 24 h. TFA was used instead of acetic acid because of its higher volatility. Work-up yielded the secondary amines as yellow oils with overall yields ranging from 6 to 49% and high HPLC purities. The synthesized amines are outlined in Table 1. In the case of 3-phenylpropylallylamine the overall yield of 49% corresponds to a yield of 85% per step. The lowest overall yield of 6% in the case of 3-phenylpropyl-3-fluorobenzylamine relates to a 60% yield per step starting from resin **9**.

In summary, we have developed a new linker system for the de novo synthesis of secondary amines on solid support. It allows for a straightforward synthesis of the desired amines in acceptable yields and high HPLC-purities.

Table 1.

Nr.	Amine	Overall-yield	HPLC-purity
8a		30%	92 %
8b		28 %	91 %
8c		23 %	92 %
8d		11 %	93 %
8e		20 %	80 %
8f		49 %	91 %
8g		28 %	85 %
8h		6 %	91 %
8i		8 %	81 %
8j		20 %	88 %

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14. General procedure: To 12.1 g of resin **9** (9 mmol loading) 150 ml anhydrous THF, 6.7 g (26 mmol) PPh_3, 26 mmol of R^1OH and 7.4 ml (38 mmol) DIAD were added and the suspension was shaken for 48 h. Then the resin was filtered off, rinsed three times with DMF, DMF/H_2O, CH_2Cl_2 and Et_2O and dried under high vacuum to give 13.6 g of **10**. This was suspended in 150 ml THF and 7.5 ml H_2O and 400 mg (18 mmol) $LiBH_4$ were added. After shaking at rt for 12 h another 400 mg (18 mmol) $LiBH_4$ was added and shaking was continued for 12 h. Work-up (see above), which comprised an additional washing step with water, gave 12.4 g of intensive yellow resin **11**. To a suspension of 5 g of **11** in 100 ml anhydrous CH_2Cl_2 4 ml (44 mmol) 3,4-dihydro-2*H*-pyran and 840 mg (4 mmol) of *p*-TsOH were added at 0°C and the mixture was shaken at 0°C for 24 h. After workup, 5.1 g of protected resin were obtained. Protected resin (1 g) was suspended in 10 ml anhydrous THF in a Schlenk-flask and 526 mg (5 mmol) KO^{t}Bu dissolved in THF were added. After 1 h the base was removed with a syringe and fresh THF (10 ml) and 5 mmol of the alkylating reagent were added. The flask was shaken for 24 h at rt. After workup 1.1–1.2 g of resin **12** was obtained. This was suspended in 15 ml TFA, 7.5 ml THF and 3.5 ml H_2O. After shaking for 24 h at 60°C the resin was filtered off and the filtrate was evaporated and taken up in CH_3CN and evaporated again (three times). After drying under high vacuum the brownish oil was dissolved in water and extracted with Et_2O (three times). After addition of 2 ml of 2 M NaOH the aqueous phase was again extracted with Et_2O (three times). Drying over $MgSO_4$, filtration and subsequent evaporation of the organic phase yielded the secondary amines as yellow highly viscous substances.