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Solid-Supported Hydrazone of 4-(4′-Formyl-3′-methoxyphenoxy)butyric Acid As a New Traceless Linker for Solid-Phase Synthesis

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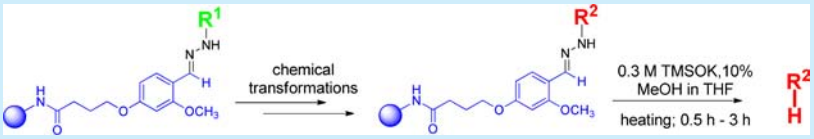
Supporting Information



ABSTRACT: The use of a hydrazine derived from a backbone amide linker as a new hydrazone-based traceless linker for solid-phase organic synthesis is described. The stability of the linker was tested under various conditions, including treatment with acids, bases, and borohydrides. Final compounds can be released by selective cleavage using trimethylsilanolate. To demonstrate the versatility of the linker, the synthesis of a model compound under various reaction conditions was performed with good results.

Solid-phase organic synthesis (SPOS) has become an important tool for the synthesis of chemical libraries over the past 20 years.[1−4]

Numerous linkers that connect a solid support to a compound of interest have been developed during this period.[5−10] To achieve this connection, a binding function must be present between the individual moieties. After the desired chemical modifications have been made, the final compound is cleaved from the solid support and bears either the original unaffected or a modified functional group, depending on the binding and cleavage type. To obtain the substrates, in which no trace of immobilization remains in the cleaved molecule, so-called traceless linkers[11−13] must be used. Thus, the purpose for a traceless linker is the formation of a C−H group at the linking site.[13]

The general problems associated with current linkers are their limited versatility under different reaction conditions and the simplicity of "binding to" and/or subsequently "cleaving from" the polymer.

Acid-sensitive silyl and germanium linkers are among the earliest developed and most useful traceless linkers.[14−16] Highly resistant sulfone linkers represent another group of traceless linkers.[17−20] The drawbacks of these linkers are poor availability and high cost of cleavage reagents (cuprate, organomalybdenum or organopalladium agents). Moreover, the final compounds may form metal ion complexes.

Azide linkers have become very popular in solid-phase chemistry.[21] In this case, alkynes are immobilized through copper-catalyzed cycloaddition. The triazole that forms can be cleaved under acidic conditions.

Hydrazone linkers belong to a very important group of traceless linkers.[22,12] Several possible cleavage conditions for hydrazones exist depending on the desired product. Reduction with borohydride leads to alkane products, whereas basic conditions afford alkenes. Thus, the use of this linker is limited to reactions with borohydrides and alcoholates.

Several other traceless linkers, such as thioether,[23] selenium,[24−26] phosphorus,[27] and tin[28] linkers, exist. However, the use of these linkers is limited for reasons similar to those described above.

Thus, SPOS still lacks easily accessible, traceless linkers with sufficient resistance toward different reaction conditions with the potential for straightforward cleavage at reaction sequence completion.

In this report, we describe a new hydrazone linker that exhibits high stability under both acidic and basic conditions, even at high temperatures. Moreover, the presence of borohydride in the reaction mixture does not affect the structure of the linker. In addition, this linker can be easily and specifically cleaved with the use of trimethylsilanolate.

Additionally, model reactions were performed to demonstrate the versatility and potential applications of this hydrazone system as a C−H traceless linker for SPOS. Hydrazones were formed from their corresponding hydrazines, which had been easily prepared via already published methods (see the Supporting Information) and used as crude materials and a commercially available, commonly used backbone amide linker (BAL, 4-(4′-formyl-3′-methoxyphenoxy)butyric acid)[29,30] that was directly bound to the common aminomethylene Merrifield resin. The model

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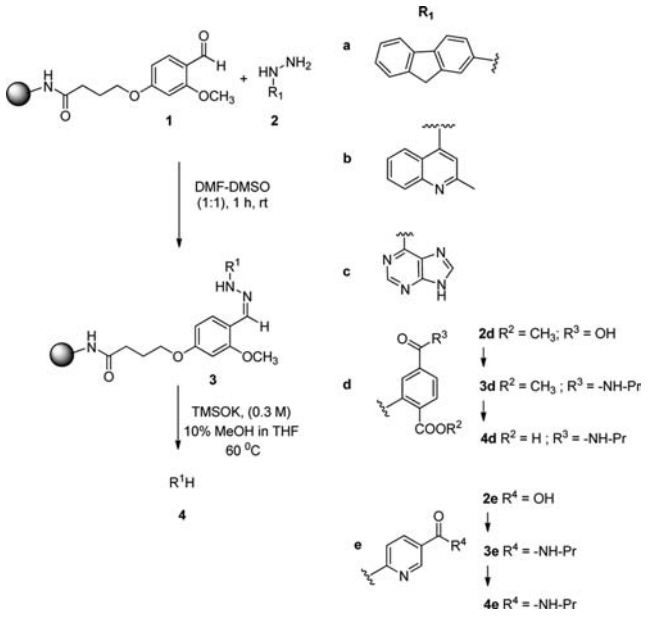
hydrazones synthesized via this condensation reaction are depicted in Scheme 1. Cleavage of the final compounds can be achieved after treatment with trimethylsilanolate in tetrahydrofuran (THF) with the addition of methanol.

Scheme 1. Synthesis of Model Hydrazones on Solid Supports



The synthetic procedure using our new linker was completed via solvent evaporation and direct high-performance liquid chromatography (HPLC) purification. This method was verified for all model compounds (**4a**–**4e**), as the hydrazones were cleaved directly after their formation and subsequently purified. The yields were calculated relative to initial aminomethylene resin loading directly in a crude mixture according to a calibration curve made with appropriate standards. The results are summarized in Table 1.

Although the cleaved compound yield does not increase after 0.5 h in some cases (**4a**, **4d**), longer reaction times are required to maximize the yields for hydrazones **4b**, **4c**, and **4e** (see Table 1).

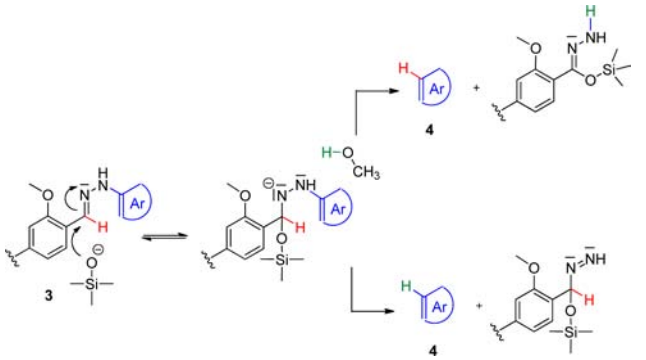
Table 1. Cleavage Conditions and Yields of Synthesized Compounds

substitution	cleavage time applied to resin **3** (h)	yield of compd **4** after cleavage (%)[a]
a	0.5	46
b	3	51
c	3	47
d	0.5	42
e	3	37

[a]Yields were determined from each compound concentration in their respective cleavage cocktail.

The reaction mechanism is difficult to explain. The ability of trimethylsilanolate to react relatively smoothly with multiple C–N bonds, demonstrated through reaction with nitriles to form amides,[31] can serve as the reaction starting point. Reductive C–N bond cleavage between hydrazine and an aromatic ring can be supported by transfer of the hydride ion, which originated from the imine group, as presented in the upper part of Scheme 2.

Scheme 2. Proposed Mechanisms for Hydrazone Cleavage



This mechanism was attempted to be proven by the synthesis of the BAL linker with a deuterated aldehyde group via modification of the previously published procedure,[32] which was converted to deuterated hydrazone **3d-*d***. Unfortunately, only nondeuterated hydrocarbon **4d** was detected via liquid chromatography–mass spectrometry (LC/MS) after cleavage.

The other possibility of a reaction mechanism is transfer of electrons from the C–N bond to a carbon of the aromatic system. The resulting anion can be stabilized by a proton from the present methanol, as presented in the lower part of Scheme 2.

To provide evidence of this mechanism, we subjected unsubstituted phenylhydrazone **3f** (Ar = phenyl) to the reaction in the presence of deuterated methanol. The phenylhydrazone was chosen to avoid any exchange of an acidic proton present in the studied aromatic part and to compare the chemical shift of deuterated benzene in NMR spectra with already published data.[33]

Although the resin for reaction was prepared very carefully to avoid the presence of any exchangeable proton outside the molecule, and thus the only NH protons can cause a decrease in isotopic yield, only nondeuterated benzene **4f** was detected by ^{1}H as well as ^{13}C NMR.

Despite the fact that the mechanism remains obscure, the cleavage time was optimized for individual structures, and the stability of the resin under various conditions was evaluated.

To determine the stability of the hydrazone linker under various conditions, the resin was treated with different reagents, including trifluoroacetic acid (TFA), organic bases, and hydroxide and borohydride solutions. The stability of the experimental control was obtained by comparing the HPLC/photodiode array (PDA) response of cleaved compound **4** before and after treatment of resin **3**, recalculated with respect to 10 mg of resin. The change in the PDA response and the maximum change of purity achieved within the cleaved compounds **4** are summarized in Table 2.

The conditions summarized in Table 2 are optimized for the time when loading remained unaffected. The maximum reaction time was 16 h. Stability over a longer time period is therefore possible; however, this reaction was not verified. Treatment with potassium hydroxide and sodium borohydride at elevated temperatures for longer reaction times caused a noticeable degradation of the polymer support.

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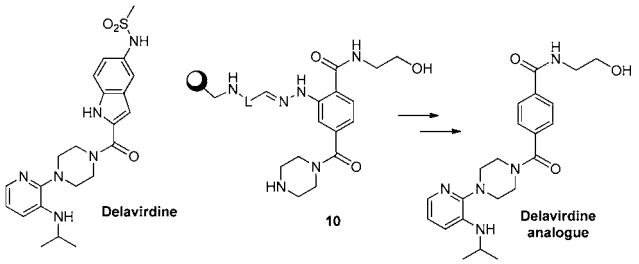
Table 2. BAL-Hydrazone Linker Stability[a]

conditions	maximum change in PDA response after treatment[b]	maximum change of purity[c]
50% TFA, rt, 3 h	4%	4%
AcOH (0.5 M), DMF, rt, 16 h	7%	6%
DIEA (0.5 M), DMF, 60 °C, 16 h	7%	7%
DBU (0.5 M), DMF, 60 °C, 16 h	7%	7%
Pyridine, 60 °C, 16 h	4%	5%
KOH, 10% (w/w), 50 °C, THF/water/MeOH (4:1:1), 3 h	4%	5%
$NaBH_4$ (0.5 M), THF, rt, 3 h	5%	5%
$NaBH_4$ (0.5 M), MeOH/THF (1:5), 50 °C, 30 min	5%	5%

[a]For detailed data see Supporting Information. [b]The change in PDA response was defined as the change in the HPLC/PDA peak area of each cleaved compound dissolved in 1 mL of solvent after treatment relative to that of the compound before treatment. Peak areas were recalculated with respect to 10 mg of resin. The maximum value belongs to the worst compound. [c]The change in purity is determined as the change before and after treatment according to HPLC analysis. The maximum value belongs to the worst compound.

To exemplify the utility of the linker, we performed the model synthesis of compound **10**, an intermediate in the synthesis of analogues derived from Delavirdine,[34] a reverse transcriptase inhibitor used in the treatment of HIV (Scheme 3). This intermediate can be subsequently transformed to the target Delavirdine analogue by a series of reactions including nucleophilic substitution of chlorine at 2-chloro-3-nitropyridine followed by reduction of a nitro group and reductive amination with acetone, which are standardly used in solid-phase synthesis.

Scheme 3. Structure of Delavirdine[35] and Example of Published Analogue[34]

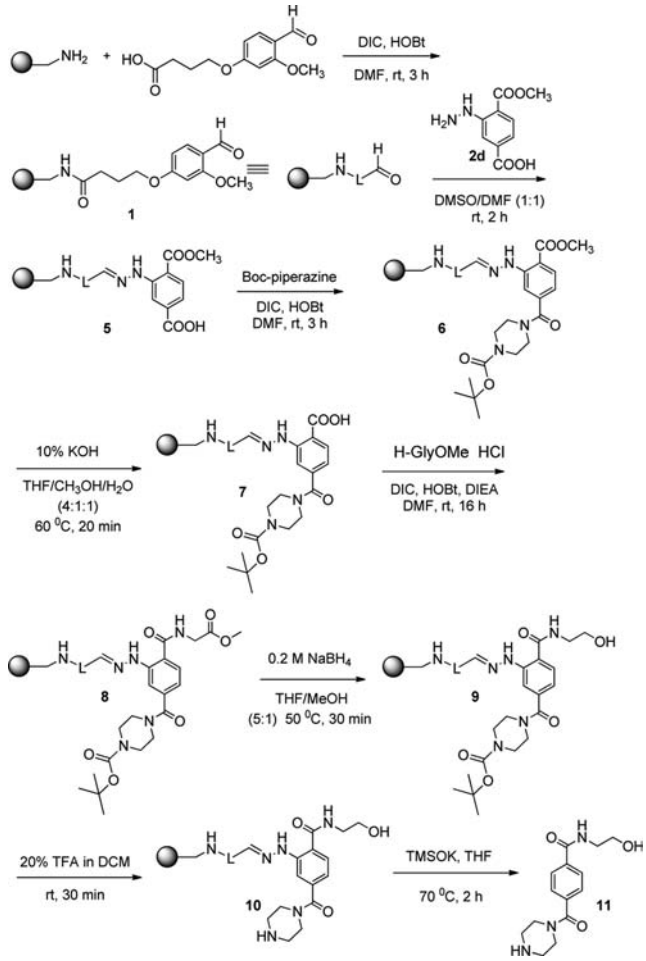


The synthetic sequence to afford derivative **11** as the cleaved product from the resin **10** (Scheme 4) included standard amide formation (providing compounds **6** and **8**), saponification under basic conditions (compound **7**), reduction with a sodium borohydride/methanol system (compound **9**), and acidic cleavage of the Boc protecting group (compound **10**). The synthesis was successfully performed with an overall yield of 15.4% relative to the initial loading of the aminomethylene resin after HPLC purification.

This result confirms that the novel hydrazone linker is stable under various reaction conditions, including heating in relatively harsh media, and is applicable in the synthesis of biologically active compounds via the combination of solid-phase synthesis and combinatorial chemistry.

In summary, we tested hydrazones derived from a commonly used BAL linker that were directly bound to an aminomethylene resin as novel hydrazone linkers for SPOS. We examined the stabilities of selected systems under various conditions, including heating in TFA, exposure to 20% KOH, and treatment with borohydrides. The hydrazones exhibited good stability under all of these conditions and can be subsequently cleaved with similar yields and purities. Therefore, the proposed linker is suitable for the synthesis of organic compounds under a wide range of reaction conditions; the synthesized compounds can then be selectively cleaved by treatment with trimethylsilanolate and subsequently purified. The utility of this novel linker was demonstrated through the synthesis of a model compound in a reaction sequence that included the aforementioned conditions. The cleaved compound yields are acceptable for high-throughput synthesis, which is used to obtain compounds rapidly and in sufficient amounts for screening regardless of yield. Elucidating the cleavage mechanism of this novel linker is the focus of future studies in this area.

Scheme 4. Model Synthesis Using the Proposed Linker



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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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