Intramolecular monomer-on-monomer (MoM) mitsunobu cyclization for the synthesis of benzofused thiadiazepinedioxides

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Abstract

The utilization of a monomer-on-monomer (MoM) intramolecular Mitsunobu cyclization reaction employing norbornenyl-tagged (Nb-tagged) reagents is reported for the synthesis of benzofused thiadiazepine-dioxides. Facile purification was achieved via ring-opening metathesis (ROM) polymerization initiated by one of three metathesis catalyst methods: (i) free metathesis catalyst, (ii) surface-initiated catalyst-armed silica, or (iii) surface-initiated catalyst-armed Co/C magnetic nanoparticles.
ROMP-derived oligomeric triphenylphosphine (OTPP) and oligomeric benzylethyl azodicarboxylate (OBEAD) reagents, as well as a monomer-on-monomer (MoM) Mitsunobu protocol, employing norborneneyl-tagged (Nb-tagged) PPh₃ and BEAD reagents. In the latter case, facile sequestration of the excess and spent reagents was achieved via ring-opening metathesis (ROM) polymerization initiated by any one of three methods utilizing Grubbs catalyst [(IMesH₂)(PCy₃)(Cl)₂Ru=CHPh cat-B]: (i) free catalyst in solution, (ii) surface-initiated catalyst-armed silica, or (iii) surface-initiated catalyst-armed carbon-coated (Co/C) magnetic nanoparticles (NPs) (Scheme 1).

The intramolecular Mitsunobu reaction has been widely utilized as a cyclization protocol for the synthesis of heterocyclic molecules. Building on these reports, we herein report the synthesis of benzo fused thiadiazepine-dioxides via an intramolecular 7-membered MoM Mitsunobu cyclization reaction, whereby facile purification was achieved utilizing ROMP sequestration initiated by free metathesis catalyst or catalyst-armed particle surfaces (Scheme 2).

The synthesis of benzo fused thiadiazepine-dioxides 3a and 3b was investigated utilizing the intramolecular MoM Mitsunobu cyclization with the readily prepared Nb-tagged PPh₃ (Nb-TPP) and DEAD (Nb-BEAD) reagents. The corresponding hydroxy-benzylsulfonamide starting materials 2a and 2b were rapidly generated via a microwave-assisted S₈Ar protocol (Scheme 3).

With sulfonamides 2a–b in hand, the application of MoM cyclization reaction was investigated utilizing Nb-TPP and Nb-BEAD (Table 1). Initially, purification was achieved by phase switching of all Nb-tagged species in solution (monomeric reagents and spent reagents) by addition of free metathesis catalyst [(IMesH₂)(PCy₃)(Cl)₂Ru=CHPh, cat-B] (Method A) to induce ROM polymerization. The ROM polymerization event was followed by precipitation to produce the desired benzo fused thiadiazepine-dioxides 3a and 3b in good yield and excellent crude purity (Table 1, entries 1–2). Purification was followed by TLC analysis, whereby the typical Mitsunobu multispot crude reaction mixture was reduced to a single spot after utilizing this polymerization sequestration protocol. Despite this success, the need for precipitation of the crude reaction mixture to remove the polymerized reagents/spent reagents was deemed not ideal for a high-throughput approach. Therefore, alternative syntheses of benzo fused thiadiazepine-dioxides 3a and 3b were investigated utilizing a catalyst-armed surface generated from either Nb-tagged Co/C magnetic particles, or Nb-tagged silica particles.

After polymerization sequestration of excess reagents/spent reagents on the surface of the magnetic Co/C beads [Method B], 3a and 3b could be obtained in reasonable crude purity by collecting the nanobeads with an external magnet, decanting the solution and evaporating the solvent (Table 1, entries 3–4). Noteworthy, this work-up procedure is carried out within a few seconds, being an operational advantage to conventional filtration techniques. However, to further improve the product purity the solution was filtered over a silica SPE. As an alternative method, the sequestration by Nb-tagged silica particles [Method C] was applied to generate 3a and 3b in comparable yields and purities with simple filtration through Celite® SPE to isolate the desired product, avoiding the need for precipitation (Table 1, entries 5–6). Building on these results, substrate scope was evaluated across all three purification sequestration protocols A–C for the synthesis of 3c–3n via MoM Mitsunobu cyclization (Scheme 4). Thus, benzo fused thiadiazepine-dioxides 3c–3f were generated with free cat-B [Method A], compounds 3g–3j via Nb-tagged Co/C magnetic particles [Method B] and benzo fused thiadiazepine-dioxides 3k–3n utilizing Nb-tagged Silica particles [Method C].
In conclusion, we have demonstrated the application of a MoM intramolecular Mitsunobu cyclization for the synthesis of bi- and tri-cyclic benzofused thiadiazepine-dioxides. Facile purification of crude reaction mixtures was achieved via ROM polymerization sequestration of excess reagents/spent reagents. This was accomplished initially utilizing free metathesis catalyst Cat-B, followed by precipitation. The method was further optimized utilizing catalyst-armed surfaces generated from either Nb-tagged Si-particles or Nb-tagged Co/C magnetic nano-particles.

Supplementary Material

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Acknowledgments

We gratefully acknowledge the National Institute of General Medical Science (Center in Chemical Methodologies and Library Development at the University of Kansas, KU-CMLD, NIH P50 GM069663 and NIH-STTR R41 GM076765) with additional funds from the State of Kansas, the International Doktorandenkolleg NANOCAT (Elitenetzwerk Bayern), the Deutsche Forschungsgemeinschaft (Re 948/8-1, "GLOBUCAT"), the Bayer-Science and Education foundation, and the EU-Atlantis program CPTUSA-2006-4560 for funding this research. We thank Materia Inc. for providing metathesis catalyst.

Notes and references


Scheme 1.
Catalyst-armed Silica- and Co/C magnetic nanoparticles.
Scheme 2.
Synthesis of benzofused thiadiazepine-dioxides via a intramolecular MoM Mitsunobu cyclization.
Scheme 3.
Synthesis of hydroxy-benzylsulfonamides 2a–b via microwave-assisted S_NAr.
Scheme 4.
Synthesis of benzofused thiadiazepine-dioxides. (3c–3f: Method A; 3g–3j: Method B; 3k–3n: Method C).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Sequestration</th>
<th>Comp.</th>
<th>Method</th>
<th>Yield (%)</th>
<th>Crude Purity (%)</th>
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<td>Cat-B</td>
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<td>A</td>
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<tr>
<td>2 b</td>
<td>Cat-B</td>
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<td>A</td>
<td>88</td>
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<tr>
<td>3 c</td>
<td>Co/C Nb-tagged</td>
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<td>87</td>
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<tr>
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<tr>
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<td>C</td>
<td>84</td>
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</table>

*Purity determined by 1H NMR.*

*Isolated via precipitation in EtOAc.*

*Isolated via magnetic decantation and filtration through Silica SPE.*

*Isolated via filtration through Celite® SPE.*