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# [4 + 2] Cycloaddition of in Situ Generated 1,2-Diaza-1,3-dienes with Simple Olefins: Facile Approaches to Tetrahydropyridazines

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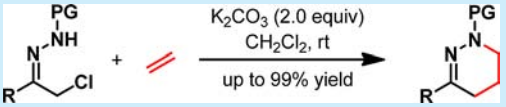
Supporting Information

**ABSTRACT:** A catalyst-free [4 + 2] annulation process between *in situ* generated 1,2-diaza-1,3-butadienes and simple olefins has been developed. Under mild conditions, the reactions afforded 1,4,5,6-tetrahydropyridazines, which feature a wide range of bioactive compounds, with high yields (up to 99% yield).




Pyridazines and tetrahydropyridazines are versatile structural motifs in a number of natural products (e.g., Pyridazomycin[1] and Azamerone[2]) and pharmaceutically active compounds (Figure 1) such as nonsteroidal progesterone receptor

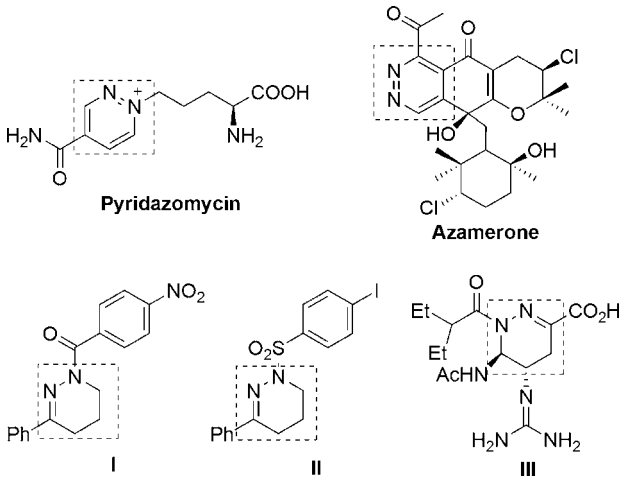
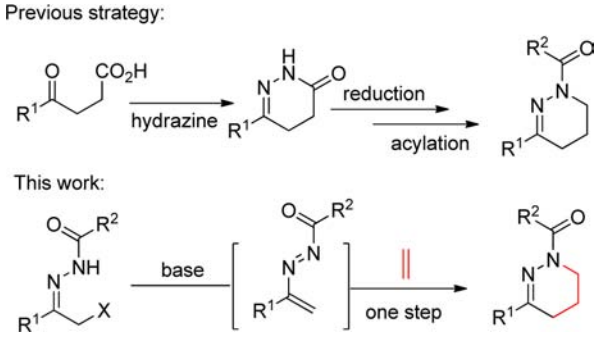



**Figure 1.** Examples of pyridazine and tetrahydro-pyridazine derivatives in bioactive compounds.

regulators (e.g., **I**),[3] neuro-transmitter inhibitors (e.g., **II**),[4] and influenza neuraminidase inhibitors (e.g., **III**).[5,6] The known synthetic strategies for the tetrahydropyridazines have been limited to a few special substrates,[7,8] and few general methods exist for their synthesis (Scheme 1).[3a,4,5] Strategically, an intermolecular [4 + 2] reaction between 1,2-diaza-1,3-dienes and alkenes is one of the most effective and economic approaches for the synthesis of tetrahydropyridazines (Scheme 1); however, such reactions are limited to those electron-rich alkenes and simple olefins remain challenging substrates.[7] In fact, [4 + 2] cycloaddition with simple olefins, especially for industrial olefins, is generally difficult to achieve and requires harsh conditions and long reaction times.[9−11]

**Scheme 1. General Strategy for Tetrahydropyridazines**




Previously, we developed an enantioselective hetero-Diels−Alder reaction of a $\beta,\gamma$-unsaturated $\alpha$-ketoester with various olefins, including cyclopentadiene,[12a] enol ethers,[12b] and simple olefins,[12c] catalyzed by asymmetric binary acids.[12d] In seeking other electron-deficient dienes for the reactions with simple olefins, we explored 1,2-diaza-1,3-dienes, generated *in situ* from $\alpha$-chloro hydrazones, e.g. $\alpha$-chloro *N*-benzoyl hydrazone **a1**, as potential targets (Scheme 1). Surprisingly, we found the reactions with olefins proceeded smoothly by simple treatment with a base in the absence of any catalysts. Herein, we present this unprecedented [4 + 2] cycloaddition of 1,2-diaza-1,3-dienes with simple olefins including those industrial olefins, affording 1,4,5,6-tetrahydropyridazines with good to excellent yields.

Initially, we have examined the reaction between **a1** and ethylene (**b1**) in the presence of metal catalysts and no reaction was observed. In this process, it was found that the use of a stoichiometric amount of $Na_2CO_3$ without any catalysts led to the desired adduct **c1** with 46% yield in $CH_2Cl_2$ (Table 1, entry 1). The base-mediated catalyst-free protocol was then optimized in terms of solvents and bases, and the representative

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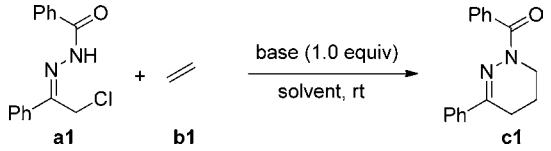
**Table 1. Optimization of the Reaction Conditions**[a]




a1 b1 c1

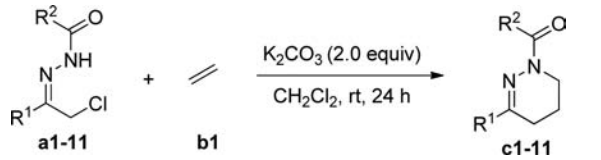
| entry | solvent | base | yield (%)[b] |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | $Na_2CO_3$ | 46 |
| 2 | $CH_3CN$ | $Na_2CO_3$ | 23 |
| 3 | $Et_2O$ | $Na_2CO_3$ | trace |
| 4 | $H_2O$ | $Na_2CO_3$ | NR |
| 5 | $CH_2Cl_2$ | $Cs_2CO_3$ | 50 |
| 6 | $CH_2Cl_2$ | $K_2CO_3$ | 68 |
| 7 | $CH_2Cl_2$ | $K_3PO_4{\cdot}3H_2O$ | 62 |
| 8 | $CH_2Cl_2$ | $Na_3PO_4{\cdot}12H_2O$ | 52 |
| 9 | $CH_2Cl_2$ | $CH_3COONa$ | 16 |
| 10 | $CH_2Cl_2$ | DIPEA | 13 |
| 11 | $CH_2Cl_2$ | $Et_3N$ | trace |
| 12 | $CH_2Cl_2$ | Pyridine | NR |
| 13[c] | $CH_2Cl_2$ | $K_2CO_3$ | 71 |
| 14[c,d] | $CH_2Cl_2$ | $K_2CO_3$ | 73 |
| 15[c,e] | $CH_2Cl_2$ | $K_2CO_3$ | 47 |
| 16[c,f] | $CH_2Cl_2$ | $K_2CO_3$ | 35 |
| 17[c,g] | $CH_2Cl_2$ | $K_2CO_3$ | trace |

[a]General conditions: **a1** (0.40 mmol), **b1** (16 atm), base (1.0 equiv), solvent (0.1 M), room temperature, 16 h. [b]Determined by $^1H$ NMR analysis with an internal standard, 1,3,5-trimethoxybenzene. [c]$K_2CO_3$ (2.0 equiv). [d]$CH_2Cl_2$ (0.2 M). [e]**b1** (10 atm). [f]**b1** (5 atm). [g]**b1** (in balloon). DIPEA = *N*,*N*-diisopropylethylamine, NR = No reaction

results are summarized in Table 1. First, screening of various solvents was carried out with $Na_2CO_3$ (1.0 equiv) at room temperature. The best result was obtained in $CH_2Cl_2$ (Table 1, entry 1), whereas others resulted in either low activity or no reaction (Table 1, entry 1 vs entries 2−4). With respect to bases, $K_2CO_3$ and $K_3PO_4{\cdot}3H_2O$ displayed better performance with improved yields (Table 1, entries 6−7), while the use of other inorganic bases resulted in a drop of the yield (Table 1, entries 1, 5, and 8−9). Organic bases, such as DIPEA, $Et_3N$, and pyridine, were ineffective (Table 1, entries 10−12). Further increasing the amount of $K_2CO_3$ (2.0 equiv) and the concentration of reaction (0.2 M) led to a slight improvement (Table 1, entries 13 and 14). The yield was significantly decreased when reducing the pressure of ethylene **b1** (Table 1, entries 15−17), and dimerization of the *in situ* generated 1,2-diaza-1,3-butadiene was observed under this condition. On the basis of these results, the combination of 0.4 mmol of **a1**, 16 atm of ethylene, and 0.8 mmol of $K_2CO_3$ in 2 mL of $CH_2Cl_2$ was identified as the optimal reaction conditions.

With the optimized conditions in hand, we next explored the substrate scope of the heterodienes. As shown in Table 2, an array of α-chloro-*N*-benzoyl hydrazones **a1**−**11** were tested, resulting in the expected 1,4,5,6-tetrahydropyridazines **c1**−**11** in good to excellent yields. The significant electronic effect of $R^2$ on the aromatic ring has been observed. Electron-neutral and -donating groups gave similar results (Table 2, entries 1−3), while electron-withdrawing groups gave relatively lower yields (Table 2, entries 5−6). An *ortho*-substituted derivative such as **a4** also worked well, providing a much better yield than its *para*-substituted counterpart (Table 2, entries 4 vs 5). Gratifyingly, the heteroaromatic 2-thiophene hydrazone **a7** and *N*-tosylhydrazone **a8** could react with ethylene, giving a 51%

**Table 2. Substrate Scope for Hydrazones**[a]




a1-11 b1 c1-11

| entry | a | $R^1$ | $R^2$ | c | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **a1** | Ph | Ph | **c1** | 73 |
| 2 | **a2** | Ph | 4-$CH_3OC_6H_4$ | **c2** | 72 |
| 3 | **a3** | Ph | 4-$CH_3C_6H_4$ | **c3** | 78 |
| 4 | **a4** | Ph | 2-$ClC_6H_4$ | **c4** | 79 |
| 5 | **a5** | Ph | 4-$ClC_6H_4$ | **c5** | 58 |
| 6 | **a6** | Ph | 4-$BrC_6H_4$ | **c6** | 40 |
| 7 | **a7** | Ph | 2-Thiophene | **c7** | 51 |
| 8 | **a8** |  | | **c8** | 48 |
| 9 | **a9** | 4-$MeOC_6H_4$ | Ph | **c9** | 56 |
| 10 | **a10** | 4-$ClC_6H_4$ | Ph | **c10** | 93 |
| 11 | **a11** | *t*-Bu | Ph | **c11** | 97 |

[a]General conditions: **a** (0.40 mmol), **b1** (16 atm), $K_2CO_3$ (2.0 equiv) and $CH_2Cl_2$ (0.2 M), room temperature, 24 h. [b]Isolated yield.

and 48% yield, respectively (Table 2, entries 7−8). Variations of the $R^1$ group were also tested, and an electron-withdrawing group was preferred to an electron-donating group (Table 2, entries 9 vs 10). In addition, alkyl substituted hydrazone **a11** worked well, leading to a 97% yield (Table 2, entry 11).

To further expand the substrate scope, we next tested other simple olefins. As seen from Scheme 2, styrenes bearing either electron-donating or -withdrawing moieties could be equally applied in the reaction with the former giving slightly better yields (Scheme 2, **c12**−**19**). Propylene **b10** and heteroaromatic 2-vinylthiophene **b11** were tolerated with 62% and 91% yields, respectively (**c20** and **c21**). α-Methylstyrene and 1,1-diphenylethylene could also be incorporated to give acceptable results by increasing the dosage and prolonging the reaction time (**c22** and **c23**). Moreover, norbornene and cyclic dienes such as norbornadiene and cyclopentadiene worked well to give the desired adducts as single diastereoisomers with high yields (**c24**, **c25**, and **c26**). An acyclic diene, isoprene, has also been examined, and the reaction afforded regioisomeric adducts **c27** and **c28** in a 1.6:1 ratio with good yields.

With *p*-methoxy-styrene, we also examined different α-chloro *N*-acylhydrazones, and the results are shown in Table 3. Hydrazones bearing either electron-donating (Table 3, entries 1−2) or electron-withdrawing groups (Table 3, entries 3−4) could be applied to give good yields. It is worth mentioning that the reaction with alkyl-substituted hydrazone **a12** also proceeded smoothly to give the desired adduct **c33** in 75% yield (Table 3, entry 5).

The developed cycloaddition could be performed on a gram scale. The reaction of α-chloro *N*-benzoyl hydrazone **a1** with ethylene **b1** afforded **c1** (1.12 g) as a nonsteroidal progesterone receptor regulator[3] in 85% yield (Scheme 3). Treatment of **c1** with $LiAlH_4$ in THF led to the reduction of the C═O bond, providing benzyl tetrahydropyridazine **d** in 64% yield (Scheme



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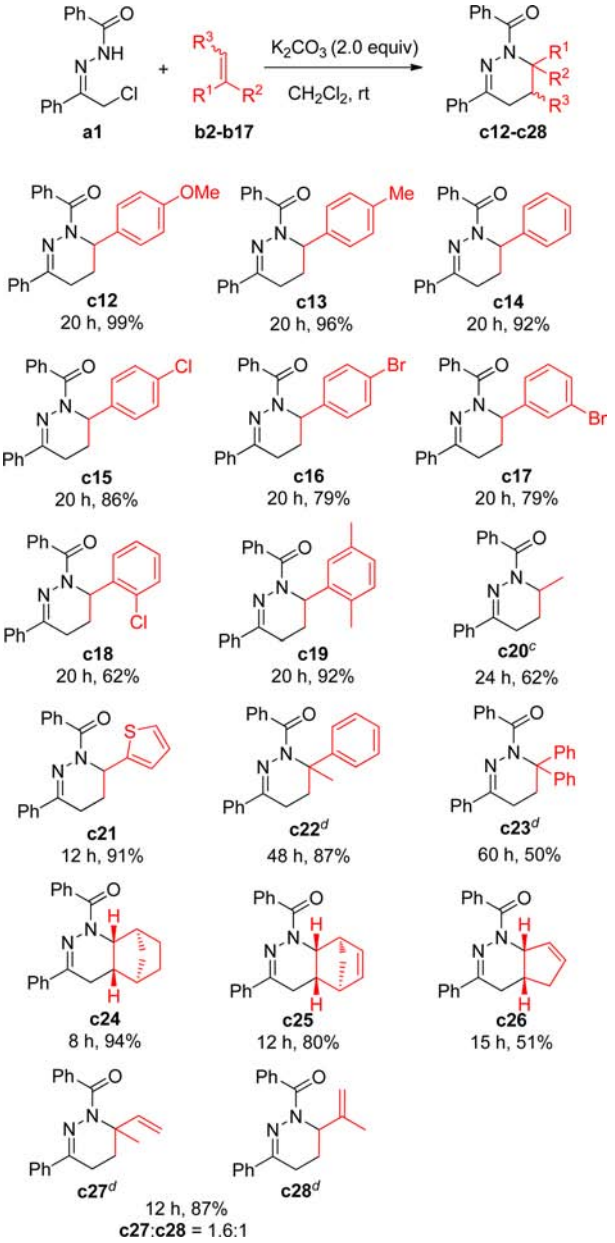
**Scheme 2. Substrate Scope for Simple Alkenes**[a,b]

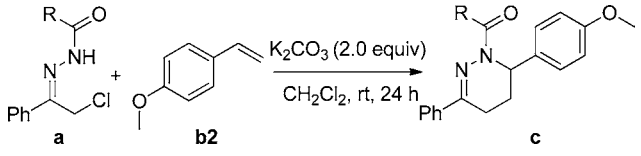



[a]General conditions: **a1** (0.40 mmol), **b** (3.0 equiv), $K_2CO_3$ (2.0 equiv) and $CH_2Cl_2$ (0.2 M), room temperature. [b]Isolated yield. [c]Propene **b10** (3 atm) was used. [d]10.0 equiv of olefin were used.

4). Direct hydrogenation of the C=N bond of **c1** could be successfully performed using Pd/C as the catalyst to give the hexahydropyridazine **e** in 78% yield, which could be further converted to a pharmaceutically important 1,4-diamine adduct **f** (Scheme 4).[13] Finally, we focused on the preparation of a pyridazine derivative through an external oxidant. When **c1** was treated with *n*-$Bu_4NI$ and TBHP in $CH_3CN$ at room temperature, the desired pyridazine **g** was isolated in 40% yield (Scheme 4).

In summary, we reported herein a mild and catalyst-free [4 + 2] cycloaddition between *in situ* generated 1,2-diaza-1,3-dienes with simple olefins. This protocol provides facile and atom-economic access to tetrahydropyridazines with good to excellent yields. Further investigations into a catalytic asymmetric version of this reaction and the extension of the methodology to other types of alkenes are ongoing.

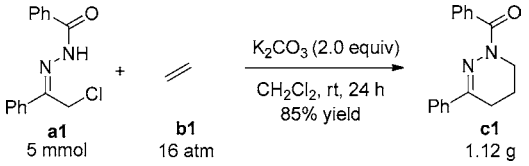
**Table 3. Substrate Scope for Hydrazones with b2**[a]



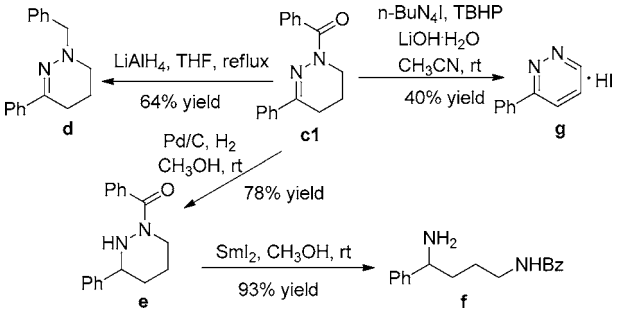

| entry | a | R | adduct | yield (%)[b] |
|---|---|---|---|---|
| 1 | **a2** | 4-$CH_3OC_6H_4$ | **c29** | 99 |
| 2 | **a3** | 4-$CH_3C_6H_4$ | **c30** | 99 |
| 3 | **a4** | 2-$ClC_6H_4$ | **c31** | 90 |
| 4 | **a6** | 4-$BrC_6H_4$ | **c32** | 66 |
| 5[c] | **a12** | *n*-$C_{11}H_{23}$ | **c33** | 75 |

[a]General conditions: **a** (0.40 mmol), **b2** (3.0 equiv), $K_2CO_3$ (2.0 equiv), and $CH_2Cl_2$ (0.2 M), room temperature, 24 h. [b]Isolated yield. [c]**b2** (5.0 equiv), 36 h.

**Scheme 3. Synthesis of c1 on a Gram Scale**




**Scheme 4. Transformation of c1**




## ■ ASSOCIATED CONTENT

### Supporting Information

General experimental procedures, characterization details, and $^1H$ and $^{13}C$ NMR spectra, IR spectra, and HRMS for new products. 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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