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# [3 + 3]-Cycloaddition of Donor–Acceptor Cyclopropanes with Nitrile Imines Generated in Situ: Access to Tetrahydropyridazines

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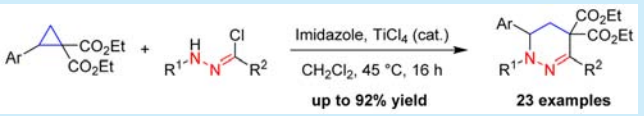
Supporting Information

**ABSTRACT:** Donor–acceptor cyclopropanes are reacted under the influence of a Lewis acid with hydrazonyl chlorides to afford tetrahydropyridazines. Formally, this transformation can be regarded as a [3 + 3]-cycloaddition of three-membered rings and nitrile imines generated in situ. This efficient method provides fast access to a variety of structurally diverse pyridazine derivatives. The structure of a typical product was confirmed by X-ray crystallography.



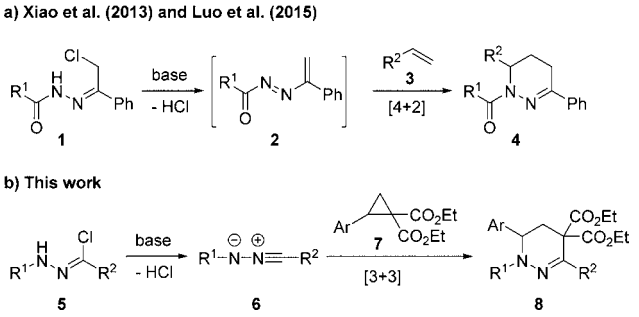

Donor–acceptor (D–A) cyclopropanes[1] have been successfully employed in heterocycle synthesis by using ring-opening,[2] rearrangement,[3] and formal cycloaddition reactions.[4] Their special reactivity is explained by the high ring strain of cyclopropanes (about 27.5 kcal/mol) and the vicinal arrangement of donor and acceptor moieties that is able to stabilize a 1,3-zwitterionic relationship.[5]

In the past decade convenient syntheses of nitrogen-containing heterocyclic compounds, which represent versatile structural motifs in natural products, pharmaceutical, and material science, have been extensively sought. D–A cyclopropanes have proven to be an excellent synthetic tool for the insertion of two-, three-, or four-atom components leading to five-, six-, or seven-membered ring systems.

Thus, the one-step synthesis of numerous five-membered nitrogen-containing heterocycles was achieved by the use of imines,[6] nitriles,[7] and diazenes.[8] The zinc-catalyzed reaction of propargyl amines and D–A cyclopropanes led to functionalized six-membered piperidines.[9] Moreover, aromatic azomethine imines deliver dihydroquinoline derivatives in a [3 + 3]-cycloaddition reaction.[10] Recently, Xu and co-workers published an inspiring synthesis of functionalized triazinines,[11] whereby the $TiCl_4$-mediated ring-opening of the cyclopropane led to an attack by azides; the resulting six-membered triazinines were converted to four-membered azetidines by simple thermolysis.

So far, no cyclopropane-based preparation of pyridazine or tetrahydropyridazine derivatives, bearing two contiguous nitrogen atoms, has been described.[12] Pyridazine and tetrahydropyridazine derivatives form the framework for several natural products and biologically active compounds.[13] Thus, tetrahydropyridazine structure motifs are found in pharmaceutically active compounds such as neurotransmitter or influenza neuraminidase inhibitors.[14] The groups of Lou and of Xiao developed a [4 + 2]-cycloaddition of in situ-generated 1,2-diaza-1,3-butadienes **2** with olefins **3** leading to tetrahydropyridazines (Scheme 1).[15] The drawback of the reaction is that it requires a large excess of the alkene (at least 7.5 equiv). Herein, we report an efficient synthesis of tetrahydropyridazine derivatives of type **8** by a [3 + 3]-cycloaddition of nitrile imines of type **6**, formed in situ, with cyclopropane 1,1-diesters **7**. Nitrile imines are generally prepared by the treatment of hydrazonyl halides with stoichiometric amounts of base.[16]

**Scheme 1. (a) Inverse Electron-Demand Hetero-Diels–Alder Reactions of Diazadienes with Olefins and (b) Our Approach for the Synthesis of Pyridazine Derivatives**




At the outset of our studies, we chose cyclopropane diester **7a** and hydrazonyl chloride **5a** as model substrates to optimize the conditions for the [3 + 3]-cycloaddition reaction. In the literature, $iPr_2NEt$ is the base of choice to generate nitrile imines from hydrazonyl chlorides.[16] As starting point the reaction was carried out in $CH_2Cl_2$ at 45 °C. Furthermore, a Lewis acid was added in catalytic amounts to trigger the opening of the three-membered ring by coordination to the ester groups. Unfortunately, $Sc(OTf)_3$, $MgI_2$, and $TiF_4$ (Table 1, entries 1–3) did not lead to any conversion of the cyclopropane diester **7a**. With $AlCl_3$ an unexpected ring-opened product **9** was found and isolated in 61% yield (entry 4). Surprisingly, no nitrile imine formation with concomitant liberation of HCl was observed. Instead, the benzene ring of the hydrazonyl chloride attacked the cyclopropane, forming a carbon–carbon bond between the 4-position of the benzene and the carbon next to the donor of the cyclopropane.

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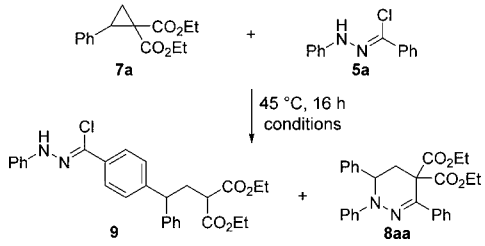
**Table 1. Optimization of the [3 + 3]-Cycloaddition Reaction to Yield Pyridazine Derivatives of Type 8aa**[a]




| entry | solvent | base | Lewis acid (20 mol %) | **8aa** yield (%) | **9** yield (%) |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | $iPr_2NEt$ | $Sc(OTf)_3$ | 0 | 0 |
| 2 | $CH_2Cl_2$ | $iPr_2NEt$ | $MgI_2$ | 0 | 0 |
| 3 | $CH_2Cl_2$ | $iPr_2NEt$ | $TiF_4$ | 0 | 0 |
| 4 | $CH_2Cl_2$ | $iPr_2NEt$ | $AlCl_3$ | 0 | 61 |
| 5 | $CH_2Cl_2$ | $iPr_2NEt$ | $TiCl_4$ | 42 | 0 |
| 6 | THF | $iPr_2NEt$ | $TiCl_4$ | 0 | 0 |
| 7 | toluene | $iPr_2NEt$ | $TiCl_4$ | 0 | 0 |
| 8 | $CH_2Cl_2$ | $NEt_3$ | $TiCl_4$ | 8 | 0 |
| 9 | $CH_2Cl_2$ | $Cs_2CO_3$ | $TiCl_4$ | mixture | |
| 10 | $CH_2Cl_2$ | pyrazole | $TiCl_4$ | 0 | 41 |
| 11 | $CH_2Cl_2$ | imidazole | $TiCl_4$ | 80 | 0 |
| 12[b] | $CH_2Cl_2$ | imidazole | $TiCl_4$ | 86 | 0 |

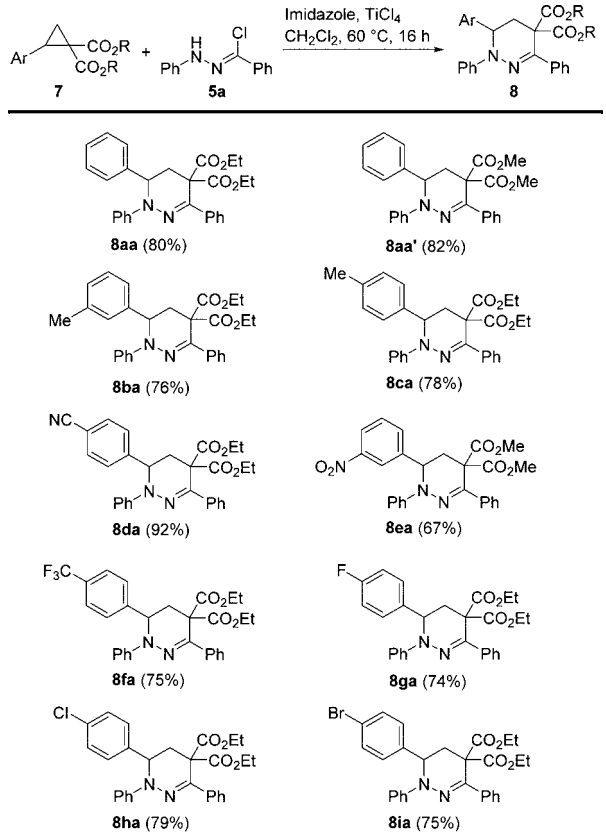
[a]Reaction conditions: **7a** (0.15 mmol), **5a** (0.10 mmol), base (0.15 mmol), Lewis acid (20 mol %), solvent (2 mL), 45 °C, 16 h; yields represent isolated products. [b]100 mol % of $TiCl_4$ was used.

The use of $TiCl_4$ as Lewis acid proved to be much more effective. In the presence of $iPr_2NEt$ in $CH_2Cl_2$ the desired tetrahydropyridazine ring was obtained in 42% yield (entry 5). A change of the solvent to THF or toluene was ineffective (entries 6 and 7). Use of triethylamine instead of $iPr_2NEt$ decreased the yield of the six-membered ring to 8% (entry 8) whereas the reaction with $Cs_2CO_3$ yielded an inseparable mixture of desired and undesired products (entry 9). Pyrazole delivered the undesired product **9** in 41% yield (entry 10). The adoption of imidazole as base brought a significant improvement, affording the tetrahydropyridazine ring in 80% yield (entry 11). By using stoichiometric amount of $TiCl_4$ the yield was further increased to a 86%. Nevertheless the following reactions were performed catalytically with 20 mol % of $TiCl_4$.

With the optimal conditions in hand, a wide range of different cyclopropanes were explored for the [3 + 3]-cycloaddition reaction. Methyl substituents in 3- or 4-position yielded the corresponding six-membered rings **8ba** and **8ca** in 76% and 78% yield, respectively (Scheme 2). Furthermore, electron-withdrawing groups in 3- and 4-position of the phenyl unit do not impact unfavorably on the ring-opening reaction. Surprisingly, the cyano group in 4-position accomplished the highest yield with 92% (**8da**). Even nitro-substituted arene rings are tolerated and afforded the pyridazine congener **8ea** in 67% yield. As we cannot explain the marked difference in yield of **8da** and **8ea** we omit any speculations. 4-(Trifluoromethyl)benzene-substituted cyclopropane yielded the desired product **8fa** in 75% yield. Nor did halogens in 4-position of the benzene ring affect the reactivity; the respective tetrahydropyridazine derivatives were successfully obtained in yields between 74% and 79% (**8ga**–**8ia**).

Subsequently, the substrate scope with respect to the hydrazonyl chloride was examined. Initially, the residue bound to the carbon atom of the hydrazonyl chloride was varied. The sterically demanding naphthyl substituent was installed at the six-membered ring (Scheme 3). Attached at 1-position of naphthyl, the yield of the product **8ab** was slightly worse (48%) than attached at 2-position (**8ac**, 59%). In contrast, the smaller benzyl group led to the desired product **8ad** in 71% yield. Moreover, the electron-donating methoxy group afforded congener **8ae** in 72% yield. However, a substitution by halogens had a serious negative influence on the reactivity. Both bromine- and fluorine-substituted congeners gave poor yields as the corresponding pyridazine derivatives **8af** and **8ag** were only obtained in 38% and 16% yields, respectively. In contrast, compound **8ah** illustrated that even heterocycles bearing a thiophene ring could be assembled (54% yield). The [3 + 3]-cycloaddition reaction also proceeded smoothly with aliphatic groups at the hydrazonyl chloride. A methyl- and even a cyclopropyl-substituted product (**8ai**–**8aj**) were obtained in good yields of 64% and 66%, respectively. In contrast, variation at the nitrogen atom of the nitrile imine precursor proved to be successful only with electron-donating groups. Methoxy- and methyl-substituted phenyl rings yielded the tetrahydropyridazines **8ak** and **8al** in 78% and 80% yield, respectively. However, electron-withdrawing substituents such as a trifluoromethyl group afforded product **8am** in only 11% yield. In the work of Lou and Xiao the installation of an acyl group at the nitrogen was a prerequisite for a successful hetero-Diels–Alder reaction. Our attempts to attach such an electron-withdrawing group at the nitrogen failed since the acyl group decreases the nucleophilicity of the intermediate nitrile imine, which is crucial for the nucleophilic attack on the

**Scheme 2. [3 + 3]-Cycloaddition Reaction with Aryl Substituted D–A Cyclopropanes**[a]




[a]Reaction conditions: **7** (0.15 mmol), **5a** (0.10 mmol), imidazole (0.15 mmol), $TiCl_4$ (20 mol %), $CH_2Cl_2$ (2 mL), 45 °C, 16 h; yields represent isolated products.



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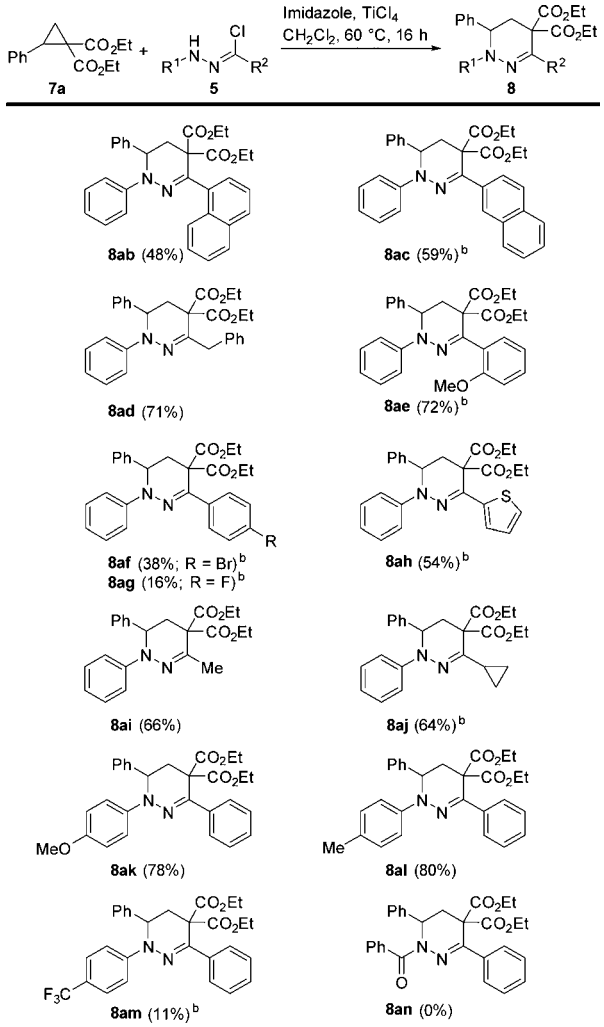
**Scheme 3. [3 + 3]-Cycloaddition Reaction with a Variety of Different Hydrazonyl Chlorides**[a]




[a]Reaction conditions: **7a** (0.15 mmol), **5** (0.10 mmol), imidazole (0.15 mmol), $TiCl_4$ (20 mol %), $CH_2Cl_2$ (2 mL), 45 °C, 16 h; yields represent isolated products. [b]100 mol % of $TiCl_4$ was used.

cyclopropane. Thus, our approach nicely complements the already existing method regarding possible substitution patterns.

To examine the viability of this methodology on a larger preparative scale, the [3 + 3]-cycloaddition reaction leading to **8aa′** was also performed on a 5.0 mmol (1.17 g) scale. The reaction with the cyclopropane dimethyl ester also proceeded very well and delivered **8aa′** in 82% yield.

To prove the formation of the six-membered ring and its regioselectivity unambiguously, we were able to grow single crystals of **8aa**. The X-ray crystallographic analysis[17,18] confirmed the anticipated structure, which is depicted in Figure 1.

These observations and literature evidence led us to propose the following mechanism, shown in Scheme 4.[11,19] The strong Lewis acid (LA) $TiCl_4$, acting as catalyst, first affords the ring-opened intermediate **10**, a 1,3-zwitterionic species. Deprotonation of the hydrazonyl chloride and the concomitant loss of HCl leads to nitrile imine **6** with a 1,3-dipolar structure. Subsequently, a nucleophilic attack, originating from the external nitrogen of the nitrile imine, forms the zwitterionic intermediate **11**. Finally, the second nucleophilic attack results in the tetrahydropyridazine derivative **8**.

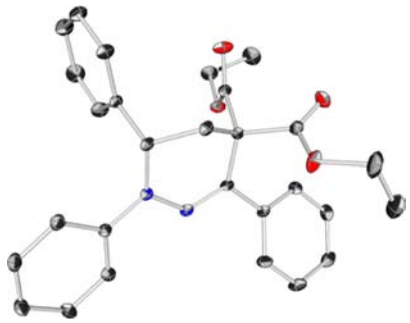
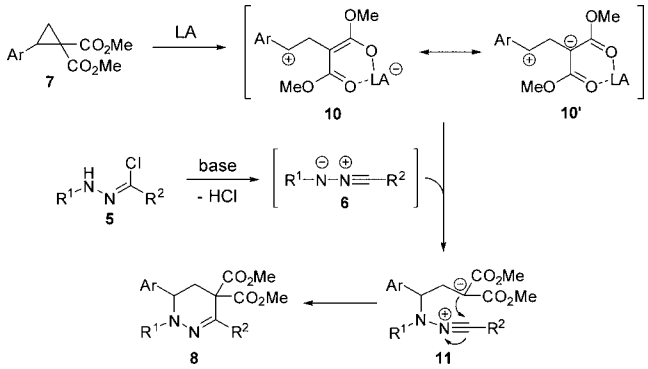


**Figure 1.** Molecular structure (50% ellipsoid probability) of **8aa** in the solid state. Oxygen atoms are shown in red, nitrogen atoms in blue. Hydrogen atoms are omitted for clarity.[16]

**Scheme 4. Proposed Reaction Mechanism**




In conclusion, we have developed the first [3 + 3]-cycloaddition reaction of D−A cyclopropanes with nitrile imines. The nitrile imines were generated in situ from hydrazonyl chlorides by treatment with imidazole. Various three-membered rings, activated by a catalytic amount of $TiCl_4$, were converted to tetrahydropyridazine derivatives. Moreover, substituents on both sides of the nitrile imines were varied. The transformations proceeded smoothly, and the desired six-membered rings were obtained in yields up to 92%. Further investigations to extend these studies to other nitrogen-containing 1,3-dipoles are ongoing.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03598.

Detailed experimental procedures and analytical data for all new compounds (PDF)
Crystal data for **8aa** (CIF)

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### Notes

The authors declare no competing financial interest.



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(18) The CIF file for **8aa** has been deposited with the Cambridge Crystallographic Data Centre as "supplementary publication no. CCDC-1442521". Copies can be obtained via email: data_request@ccdc.cam.ac.uk.

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