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Nickel(0)-Catalyzed [3+2] Cycloadditions of Bis(alkylidenecyclopropanes) with Diazenes: A Facile Synthesis of Functionalized Pyrazolidine-1,2-dicarboxylates

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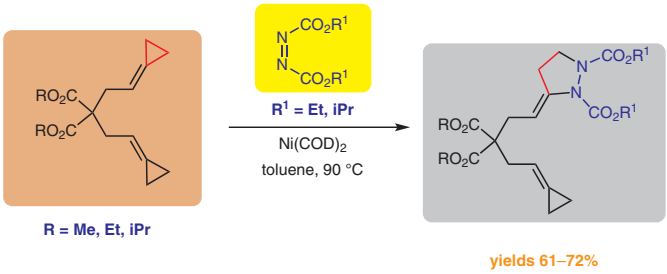

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Abstract A nickel(0)-catalyzed intermolecular [3+2] cycloaddition of bis(alkylidenecyclopropanes) with diazenes such as diethyl or diisopropyl azodicarboxylate gave pyrazolidine-1,2-dicarboxylates in moderate to good yields (61–72%).

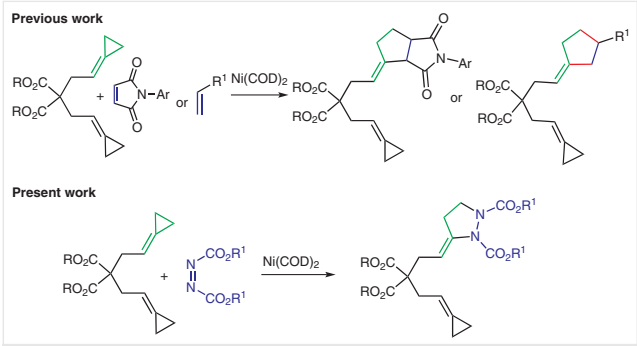
Keywords bisalkylidenecyclopropanes, diazenes, pyrazolidine-dicarboxylates, [3+2] cycloaddition, nickel catalysis

Metal-catalyzed [*m*+*n*] cycloaddition reactions are effective tools for the synthesis of carbo- and heterocyclic systems.[1] Functionalized cyclopropanes have been exploited in metal-catalyzed [*m*+*n*] cycloadditions for the synthesis of monocyclic or condensed carbocycles.[2–4] There are also reports on cycloadditions of activated cyclopropanes with heterodienophiles for the synthesis of monocyclic or condensed carbo- and heterocycles.[2–4] De Meijere and coworkers explored the Lewis acid-catalyzed [3+2] cycloadditions of 2-arylcyclopropane-1,1-dicarboxylates with diazenes to afford functionalized pyrazolidines.[5] However, [*m*+*n*] cycloadditions of functionalized nonactivated cyclopropanes, especially with heterodienophiles, have rarely been reported in the literature.[2c,d,6,7]

Pyrazolidines have been evaluated as antibacterial, antifungal, anticancer, antidepressant, antiinflammatory, antituberculosis, antioxidant, and antiviral agents in various pharmacological studies.[8] Several pyrazolidine-based drugs have been marketed, including the antiinflammatory drug celecoxib, rimonabant for the treatment of obesity, fomepizole as an effective alcohol dehydrogenase inhibitor, and sildenafil as a phosphodiesterase inhibitor.[9] Pyrazolidines are also useful as chiral auxiliaries and as synthetic reagents in multicomponent reactions.[10] In addition, natural products containing pyrazolidine moieties have been shown to have pharmacological properties.[11]

Conventional approaches, such as the condensation of 1,3-dicarbonyl compounds with hydrazines or [3+2] cycloadditions of 1,3-dipoles have been used in syntheses of simple pyrazolines.[12] However, there are few reports on synthesis of functionalized pyrazolidines. Chaudhry et al. recently reported acid-catalyzed cyclizations using allylic hydrazines for the synthesis of pyrazolidines.[13]

In view of these results and our ongoing interest in the cycloaddition chemistry of functionalized cyclopropanes, we wish to report an extension of our nickel(0)-catalyzed [3+2]-cycloadditions of bis(alkylidenecyclopropanes) to the preparation of pyrazolidines by using diazenes (Scheme 1).[7]



Scheme 1 [3+2]-Cycloadditions of bis(alkylidenecyclopropanes)

In the present work, we examined the [3+2] cycloadditions of bis(alkylidenecyclopropanes) with diazenes such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) as dienophiles (Scheme 1). The reaction

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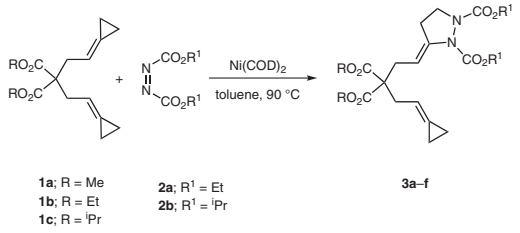
resulted in the formation of functionalized cyclopropane-tethered pyrazolidine-1,2-dicarboxylates in good yields.

The bis(alkylidenecyclopropane) reactants **1a–c** were synthesized by treating the appropriate dialkyl malonates with 1-vinylcyclopropyl tosylate by using the reported procedure.[14] We examined the cycloaddition reactions of the bis(alkylidenecyclopropanes) **1a–c** with azodienophiles in the presence of nickel(0) complexes as catalysts. Importantly, the cycloaddition reactions with the diazenes DIAD and DEAD resulted in the formation of [3+2] cycloadducts, and no competitive [3+2+2] or [3+3+2] cycloadditions were observed.[15] The [3+2] cycloadditions occurred by preferential ring opening at the allylic position of one of the methylenecyclopropane groups of the 2,2-bis(2-cyclopropylideneethyl)malonates **1a–c** to afford the corresponding pyrazolidinene-1,2-dicarboxylates **3a–f** in good yields.

Treatment of dimethyl bis(2-cyclopropylideneethyl)malonate (**1a**) with DEAD (**2a**) in toluene at various temperatures did not result in cycloaddition, and the starting material was recovered (Table 1, entries 1 and 2). The [3+2] cycloaddition of 1a with DEAD (**2a**) was then examined in the presence of $Ni(COD)_2$ as catalyst under various conditions (entries 3–13). The reaction proceeded smoothly leading to the formation of diethyl (3*E*)-3-(5-cyclopropylidene-3,3-bis(methoxycarbonyl)pentylidene)pyrazolidine-1,2-dicarboxylate (**3a**) in good yields (entries 4–10). However, the [3+2] cycloaddition did not occur in the presence of the ligands PPh_3, DPPE, or $P(OEt)_3$ when $Ni(COD)_2$ was used as the catalyst (entries 11–13). The use of fewer equivalents of DEAD led to lower yields due to nonproductive decomposition of DEAD (entries 4 and 5). Poor yields were observed in the polar aprotic solvent DMF, as well as in dichloroethane (DCE) or 1,4-dioxane (entries 8–10). Optimal conversion was obtained by using 10 equivalents of DEAD[16] at 90 °C with toluene as solvent (entry 6).

After optimization of the reaction conditions, the [3+2]-cycloadditions of various dialkyl 2,2-bis(2-cyclopropylideneethyl)malonates with diazodienophiles using $Ni(COD)_2$ were explored (Scheme 2). These reactions resulted in the formation of functionalized pyrazolidine-1,2-dicarboxylates **3a–f** in moderate to good yields (Table 2).[17] No significant change in the yield of the reaction was observed on changing the substrate or the dienophile.



Scheme 2 Nickel-catalyzed [3+2]-cycloaddition of bis(alkylidenecyclopropanes) **1a–c** with dialkyl azodicarboxylates **2a** and **2b**

The resulting [3+2] products were characterized by spectroscopic analysis.[18] Diethyl (3*E*)-3-[5-cyclopropylidene-3,3-bis(isopropoxycarbonyl)pentylidene]pyrazolidine-1,2-dicarboxylate (**3c**), for example, showed an $[M + H]^+$ ion at *m/z* 495.3 in its mass spectrum. The ^1H NMR (300 MHz) spectrum showed two characteristic multiplets at 5.61 and 5.57 ppm, corresponding to protons H_2 and H_3 re-

Table 1 Optimization of the Reaction Conditions for the [3+2] Cycloaddition of Dimethyl 2,2-Bis(2-cyclopropylideneethyl)malonate (**1a**) with Diethyl Azodicarboxylate (**2a**)

Entry	Catalyst	Ligand (1 equiv)	DEAD (equiv)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	–	–	10	toluene	40	24	0[b]
2	–	–	10	toluene	120	24	0[b]
3	$Ni(COD)_2$	–	10	toluene	40	24[c]	10
4	$Ni(COD)_2$	–	1	toluene	90	16	15
5	$Ni(COD)_2$	–	5	toluene	90	16	34
6	$Ni(COD)_2$	–	10	toluene	90	16	72
7	$Ni(COD)_2$	–	10	toluene	120	16	69
8	$Ni(COD)_2$	–	10	1,4-dioxane	90	20	48
9	$Ni(COD)_2$	–	10	DMF	110	24	22
10	$Ni(COD)_2$	–	10	DCE	70	24	24
11	$Ni(COD)_2$	PPh_3	10	toluene	120	24	0
12	$Ni(COD)_2$	DPPE	10	toluene	120	24	0
13	$Ni(COD)_2$	$P(OEt)_3$	10	toluene	120	24	0

[a] Isolated yield after purification.
[b] The starting material was recovered.
[c] Incomplete reaction.

Table 2 Nickel-Catalyzed [3+2]-Cycloaddition Reactions of Bis-(alkylidenecyclopropanes) **1a–c** with Dialkyl Azodicarboxylates[a]

Entry	R^1	R^2	Product	Yield[b] (%)
1	Me	Et	**3a**	72
2	Et	Et	**3b**	70
3	*i*-Pr	Et	**3c**	61
4	Me	*i*-Pr	**3d**	68
5	Et	*i*-Pr	**3e**	67
6	i-Pr	*i*-Pr	**3f**	68

[a] Reaction in toluene at 90 °C for 16 h.
[b] Isolated yield after purification.

spectively (Figure 1). A characteristic multiplet at 3.70 ppm corresponded to H_1 and two doublets of doublets at 1.05 ppm (J = 4.5 Hz) and 1.02 ppm (J = 4.5 Hz) were assigned to the H_4 and H_5 protons of the cyclopropyl ring, respectively. The ^{13}C NMR spectrum showed the presence of two carbonyl carbons at 170.6 and 156.4 ppm corresponding to the isopropyl ester carbonyl and carbamate ester carbonyl, respectively. The ^{13}C NMR spectrum also showed the presence of two olefinic carbons at 115.7 and 111.9 ppm, corresponding to C2 and C3, respectively, and two aliphatic carbons at 2.8 and 2 ppm, corresponding to C4 and C5, respectively (Figure 1).

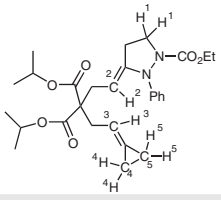
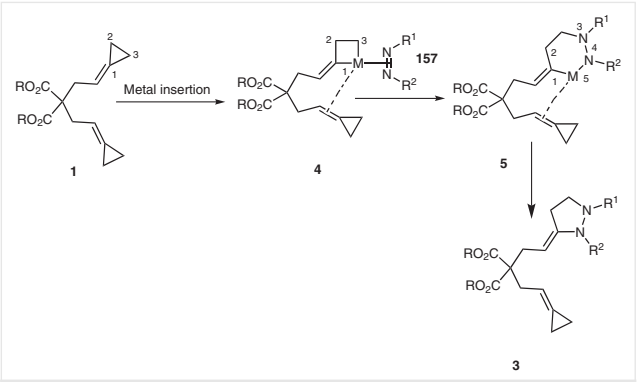


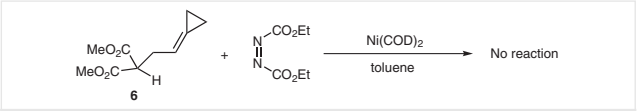
Figure 1 Diethyl (3*E*)-3-[5-cyclopropylidene-3,3-bis(isopropoxycarbonyl)pentylidene]pyrazolidine-1,2-dicarboxylate (**3c**)

A plausible mechanism for the metal-catalyzed cycloaddition involves an initial oxidative addition of the metal complex to the proximal bond of one of the methylene cyclopropanes of **1** to afford metallacyclobutane **4**. This is followed by oxidative insertion of the dialkyl azodicarboxylate to afford metallacycle **5**. The intermediates **4** and **5** are stabilized by coordination of the π-electrons of neighboring alkylidenecyclopropane moiety with the metal in a metallacyclobutane. The coordination of the metal in the metallacyclobutanes **4** and **5** with the neighboring cyclopropane alkene bond is deemed critical for the formation of functionalized pyrazolidine product **3**. Finally, intermediate **5**, upon reductive elimination, furnishes the [3+2]-cycloadduct product **3** (Scheme 3).



Scheme 3 Plausible mechanism for the formation of **3**

Evidence that the presence of the second alkylidenecyclopropane is crucial for the success of these [3+2] cycloadditions came from the observation that the monoalkylidene compound **6** did not react in this manner, and no bisadducts were obtained (Scheme 4).



Scheme 4

In conclusion, we have developed an intermolecular [3+2] cycloaddition of previously unexplored bis-(alkylidenecyclopropanes) with diazenes mediated by a nickel(0) catalyst. The diazenes DIAD and DEAD were used in these intermolecular [3+2]-cycloaddition reactions, resulting in the formation of functionalized pyrazolidine-1,2-dicarboxylates in moderate to good yields. Further work exploring the application of transition metals in [*m*+*n*] cycloadditions of bis(alkylidenecyclopropanes) is in progress.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691502.

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(16) An excess of the azodienophile is used to compensate for its thermal decomposition during the reaction.

(17) **[3+2]-Cycloadducts 3a–f; General Procedure**
Dialkyl azodicarboxylate **2** (2 mmol, 10 equiv) was added to a solution of the appropriate bis(alkylidenecyclopropane) **1** (0.2 mmol, 1 equiv) in toluene (4 mL), and the mixture was degassed for 10 min under argon. $Ni(COD)_2$ (5 mol%) was added, and the mixture was heated to 90 °C for 16 h. After completion of the reaction, the mixture was cooled to r.t., directly loaded onto a column without evaporation, and purified by flash chromatography [silica gel (100–200 mesh), EtOAc–hexanes].

(18) **Diethyl (3*E*)-3-[5-Cyclopropylidene-3,3-bis(methoxycarbonyl)pentylidene]pyrazolidine-1,2-dicarboxylate (3a)**
Colorless liquid; yield: 119 mg (72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.71 (m, 1 H), 5.48 (m, 1 H), 4.13–4.20 (m, 4 H), 3.71 (s, 6 H), 3.65 (m, 2 H), 2.75 (d, *J* = 9, Hz, 2 H), 2.49 (br s, 2 H), 2.01 (m, 2 H), 1.22–1.27 (m, 6 H), 0.99 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 156.3, 137.7, 126.9, 116.0, 112.3, 61.5, 57.7, 52.1, 46.7, 37.0, 35.5, 29.3, 14.6, 2.6, 2.0. LRMS (ESI): *m/z* = 439.2 [M + H]$^+$. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{21}H_{31}N_2O_8$: 439.2080; found: 439.2067.
Diethyl (3*E*)-3-[5-Cyclopropylidene-3,3-bis(isopropoxycarbonyl)pentylidene]pyrazolidine-1,2-dicarboxylate (3c)
Pale-yellow liquid; yield: 94 mg (61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.61 (m, 1 H), 5.57 (m, 1 H), 5.03 (m, 2 H), 4.19 (m, 4 H), 3.70 (m, 2 H), 2.76 (d, *J* = 7.2 Hz, 2 H), 2.66 (bs, 2 H), 1.78 (m, 2 H), 1.20–1.32 (m, 18 H), 1.05 (t, *J* = 4.5 Hz, 2 H), 1.02 (t, *J* = 4.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 155.6, 137.7, 126.2, 115.5, 112.1, 69.0, 62.4, 57.0, 46.1, 37.8, 35.8, 29.6, 21.5, 14.5, 2.8, 2.0. LRMS (ESI): *m/z* = 495.3 [M + H]$^+$. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{39}N_2O_8$: 495.2706; found: 495.2718.