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Lewis acid-mediated [3+2] cycloaddition between hydrazones and olefins

Shū Kobayashi,* Ryoji Hirabayashi, Haruka Shimizu, Haruro Ishitani and Yasuhiro Yamashita

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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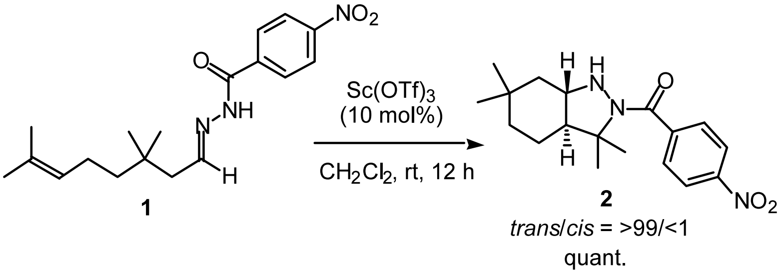
Abstract—[3+2] Cycloaddition between hydrazones and olefins was accelerated in the presence of a stoichiometric amount of $BF_3·OEt_2$ or a catalytic amount of $Zr(OTf)_4$, $Hf(OTf)_4$, or $Sc(OTf)_3$ under mild conditions. The corresponding pyrazolidine derivatives were obtained in moderate to high yields using this novel [3+2] Lewis acid catalysis. © 2003 Elsevier Science Ltd. All rights reserved.

[3+2] Cycloaddition is one of the most useful reactions providing five-membered cyclic compounds.[1] While [3+2] cycloaddition using nitrones and nitrile oxides has been intensively studied,[2] the corresponding reactions of hydrazones with olefins affording pyrazolidines have not been well investigated.[3] In 1970, Hesse reported that aldehydes reacted with hydrazines at first and then with styrene derivatives to afford pyrazolidines in acetic acid in the presence of sulfonic acid.[4] In 1978, Grigg et al. reported that cycloaddition between hydrazones and olefins having electron-withdrawing groups proceeded under thermal conditions (in xylene at 150°C).[5] In these examples, substrates applicable are rather limited, and drastic conditions such as strongly acidic and thermal conditions are required.[6,7] Our idea was to utilize Lewis acids in [3+2] cycloaddition between hydrazones and olefins, and to attain this transformation under milder conditions.

First, we tested an intramolecular [3+2] cycloaddition of hydrazone/olefin **1**, and found that a catalytic amount of $Sc(OTf)_3$ was quite effective in this transformation to give the pyrazolidine derivative **2** in high yield with high stereoselectivity (Scheme 1).[8] Besides $Sc(OTf)_3$, $Zr(OTf)_4$ also catalyzed this reaction effectively in quantitative yield with exclusive *trans* selectivity (>99/<1).

We then examined an intermolecular [3+2] cycloaddition between acylhydrazone **3a** derived from ethyl glyoxylate and cyclopentadiene (CP, **4a**). While $Sc(OTf)_3$ also gave the desired product in moderate yield, it was found that $Zr(OTf)_4$ or $Hf(OTf)_4$ gave better yields in this cycloaddition (Table 1). When 10 mol% of $Zr(OTf)_4$ and $Hf(OTf)_4$ was used in dichloromethane, the corresponding [3+2] cycloaddition adduct was obtained in 73% and 69% yields, respectively, with high



Scheme 1. Lewis acid-catalyzed intramolecular [3+2] cycloaddition of a hydrazone/olefin.

Keywords: [3+2] cycloaddition; hydrazone; Lewis acid; intramolecular; intermolecular.

* Corresponding author. Fax: +81 3 5634 0634; e-mail: skobayas@mol.f.u-tokyo.ac.jp

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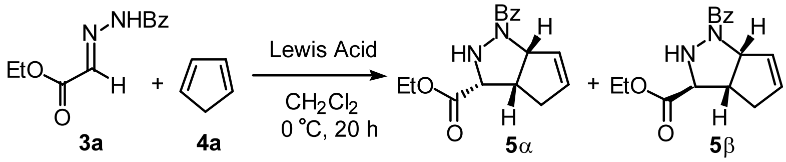
Table 1. Intermolecular [3+2] cycloaddition reactions of a hydrazone with cyclopentadiene



Entry	Lewis acid (equiv.)	Yield (%)	dr[a] (**5α**/**5β**)
1	$Sc(OTf)_3$ (0.20)	46	89/11
2	$Zr(OTf)_4$ (0.20)	46	>99/<1
3	$Zr(OTf)_4$ (0.10)	73	94/6
4	$Zr(OTf)_4$ (0.05)	62	95/5
5	$Hf(OTf)_4$ (0.20)	57	98/2
6	$Hf(OTf)_4$ (0.10)	69	94/6
7	$Hf(OTf)_4$ (0.05)	57	96/4
8[b]	$BF_3{\cdot}OEt_2$ (1.10)	93	86/14

[a] Each diastereomer was isolated.

[b] 4 h.

diastereoselectivities (**5α**/**5β**=94/6, in entries 3, 6).[9] Lower yields were obtained when the amounts of the Lewis acids were increased (20 mol%) or decreased (5 mol%). For solvents, dichloromethane gave the best result, while THF (40% yield), acetonitrile (50%), toluene (21%), and DMF (0%) were less effective (in the reaction of **3a** with CP using 10 mol% of $Zr(OTf)_4$). On the other hand, the use of a stoichiometric amount of $BF_3{\cdot}OEt_2$ gave the desired product in 93% yield with lower diastereoselectivity.

Other substrates were then tested, and the results are summarized in Table 2. Benzoylhydrazone **3b** derived from 3-phenylpropionaldehyde reacted with CP in the presence of a catalytic amount of $Zr(OTf)_4$ to form [3+2] cycloadduct in good yield (entry 1). On the other hand, benzoylhydrazone **3c** derived from benzaldehyde was found to be less reactive, and the desired cycloaddition proceeded in the presence of a stoichiometric amount of $BF_3{\cdot}OEt_2$ (entry 2). Other dienophiles also worked well under the reaction conditions. The cycloaddition between hydrazone **3a** and α-methylstyrene (**4b**) gave two diastereomers in moderate yield with good selectivity (entry 3). In this combination, an ene-type reaction also occurred to give product **6** in 12% yield. In the reaction of **3a** with 2-methyl-1,3-butadiene (**4c**), competitive reactions between [3+2] cycloaddition and [4+2] aza Diels–Alder reaction occurred to afford the desired pyrazolidine derivative and the Diels–Alder adduct **7** in 37% and 28% yields, respectively (entry 4). On the other hand, the desired [3+2] cycloaddition reactions proceeded exclusively, and no [4+2] cycloadduct was observed in the reactions with ene–yne compounds (**4d**–**f**) (entries 5–7).

A typical experimental procedure is described for the [3+2] cycloaddition between hydrazone **3a** and CP in the presence of 0.10 equivalent of $Zr(OTf)_4$ (Table 1, entry 3). To a suspension of $Zr(OTf)_4$ (0.030 mmol) and **3a** (0.30 mmol) in dichloromethane (1.0 mL) was added CP (0.9 mmol) at 0°C, and the whole was stirred for 20 h at the same temperature. After quenching with saturated $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The organic layers were combined and washed with brine, and dried over anhydrous $MgSO_4$. After filtration and concentration under reduced pressure, the crude mixture was purified by preparative thin-layer chromatography (silica gel) to afford the desired diastereomers of the cycloadduct in 73% yield (the diastereomer ratio was 94/6).

In summary, we have found that [3+2] cycloaddition between hydrazones and olefins was accelerated by Lewis acids. A stoichiometric amount of $BF_3{\cdot}OEt_2$ or a catalytic amount of $Zr(OTf)_4$, $Hf(OTf)_4$, or $Sc(OTf)_3$ was found to be effective in this cycloaddition, and the desired pyrazolidine derivatives were obtained in moderate to high yields. This novel Lewis acid catalysis enables the cycloaddition pathway to proceed under milder conditions compared with those in conventional protocols. Chiral Lewis acid catalysis of this unique [3+2] cycloaddition may be the next goal, and further investigations along this line are now in progress.

Acknowledgements

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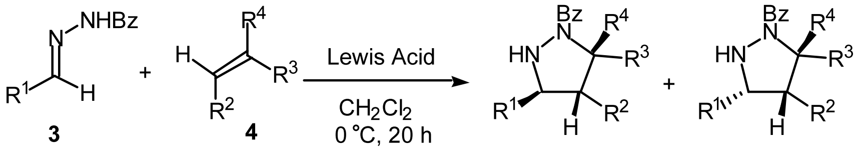
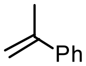
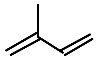
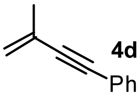
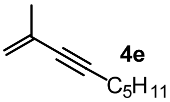
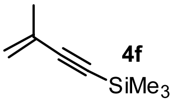
Table 2. Intermolecular [3+2] cycloaddition reactions of hydrazones with olefins



Entry	R^1	Olefin	Lewis Acid (eq.)	Yield (%)	dr[a]
1	$PhCH_2CH_2$ (**3b**)	 **4a**	$Zr(OTf)_4$ (0.10)	61	—[b]
2	Ph (**3c**)	 **4a**	$BF_3{\cdot}OEt_2$ (1.20)	67	—[b]
3	EtOOC (**3a**)	 **4b**	$BF_3{\cdot}OEt_2$ (1.20)	58[c]	85/15
4[d]	EtOOC (**3a**)	 **4c**	$BF_3{\cdot}OEt_2$ (1.20)	37[e]	68/32
5[d]	EtOOC (**3a**)	 **4d**	$BF_3{\cdot}OEt_2$ (1.20)	77	56/44
6[d]	EtOOC (**3a**)	 **4e**	$BF_3{\cdot}OEt_2$ (1.20)	70	57/43
7[d]	EtOOC (**3a**)	 **4f**	$BF_3{\cdot}OEt_2$ (1.20)	43	79/21

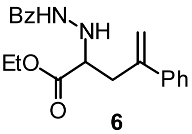
[a] Diastereomer ratio was determined by ^1H NMR, and relative configuration was not established.

[b] Not determined.

[c] 18 h. Ene-type product **6** was obtained (12%).

[d] The reaction was carried out at room temperature.

[e] Aza Diels–Alder adduct **7** was obtained (28%).



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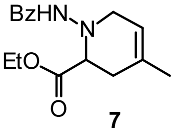

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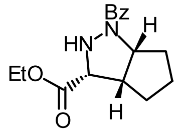
9. The relative configuration of **5α** was determined by X-ray crystal structure analysis of hydrogenated **5α** (**8**).



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