Tetrahedron Letters 53 (2012) 182–185

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$InBr_3$ catalyzed three-component reactions of an aryldiazoacetate, an alcohol, and a carbonyl compound

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ARTICLE INFO

Article history:
Received 28 August 2011
Revised 24 October 2011
Accepted 3 November 2011
Available online 9 November 2011

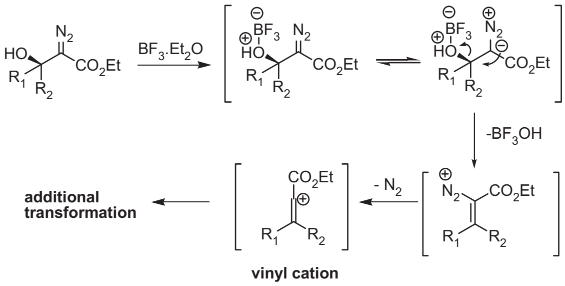
Keywords:
Lewis acid
Indium tribromide
Diazo decomposition
Oxonium ylide
Three-component reaction

ABSTRACT

$InBr_3$ promoted three-component reactions of an aryldiazoacetate, an alcohol, and an electron deficient carbonyl compound gave α,β-dihydroxyl acid derivatives in good yield with high diastereoselectivity. The reaction is proposed through a protic oxonium ylide trapping process. The reaction mechanism for the formation of the protic oxonium ylide via Lewis acid $InBr_3$ catalyzed diazo decomposition is suggested through a vinyl cationic intermediate.

Transition-metal catalyzed diazo decomposition through a carbenoid intermediate plays an important role in organic synthesis.[1] Rhodium and copper complexes are the most widely used transition-metal catalysts for the diazo decomposition.[2] In addition, some other transition metals such as Pd,[3a] Ni,[3b] Ru,[3c] Co,[3d] and Fe[3e,f] have been reported to catalyze diazo decomposition reactions. In contrast, less attention has been paid to use Lewis acids to successfully catalyze diazo decomposition.[4] This is partially because Lewis acids are commonly considered to be compatible to diazo compounds, and they are mostly employed as catalysts to activate other electrophilic substrates in the reaction that involves diazo compounds. Nevertheless, some Lewis acids with stronger Lewis acidity have been reported to catalyze diazo decomposition via reaction pathways other than metal carbenoid.[4a,b] For example, Padwa et al. reported Lewis acids (such as $BF_3{\cdot}Et_2O$) catalyzed decomposition of α-hydroxyl diazoacetate, in which, the reaction was proposed through a vinyl cationic intermediate (Scheme 1).[4a] We have reported novel transition-metal catalyzed three-component reactions of a diazo compound, an alcohol, and an electrophile to give polyfunctional molecules in an efficient fashion.[5] A protic oxonium ylide, that is in situ generated from a metal carbenoid and an alcohol, was proposed as an intermediate in the reaction. We report here the first example of employing Lewis acid $InBr_3$ to successfully catalyze such a three-component reaction. Thus, diazo decomposition reactions of an aryldiazoacetate, an alcohol with an electron deficient carbonyl compound occurred in the presence of $InBr_3$ to afford three-component α,β-dihydroxyl acid derivatives efficiently.

We have recently shown that $InBr_3$ served as an effective additive helping to control the diastereoselectivity in $Rh_2(OAc)_4$ catalyzed three-component reactions of an aryldiazoacetate, an alcohol, and a β,γ-unsaturated α-keto ester.[6] Since $InBr_3$ was reported to be an effective catalyst for the diazo decomposition,[4d] we wondered if $InBr_3$ alone can promote the three-component reaction. We first examined $InBr_3$ catalyzed O–H insertion of a diazo compound and an alcohol, because this reaction can provide useful information regarding protic oxonium ylide formation. It was found that when an electron donating aryldiazo acetate, such as methyl *para*-methoxyphenyl diazoacetate (**1a**), was used as a substrate, $InBr_3$ catalyzed reaction with BnOH gave the corresponding O–H insertion product **9a** in a 60% yield. No reaction occurred when an electron



Scheme 1. Lewis acid catalyzed diazo decomposition proposed by Padwa.[4a]

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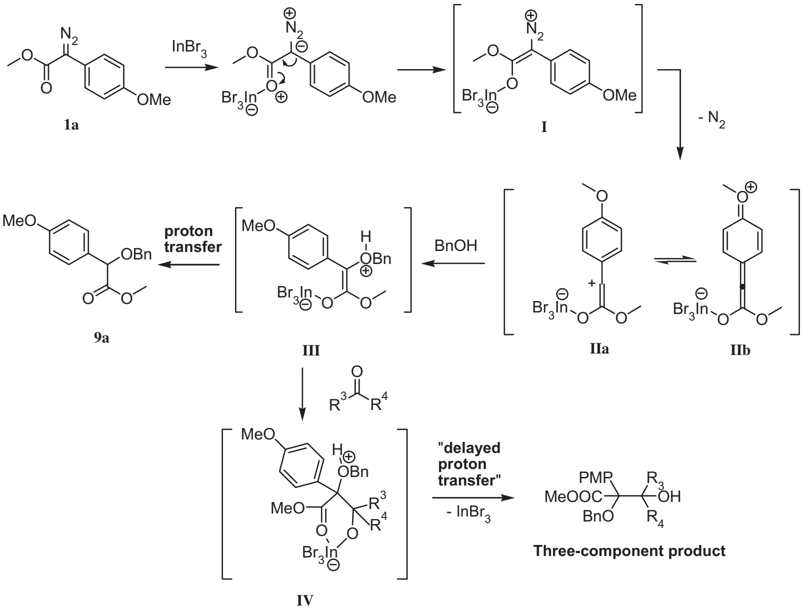
doi:10.1016/j.tetlet.2011.11.005

withdrawing aryldiazoacetate was used in the O–H insertion reaction. A possible reaction pathway for the O–H insertion was suggested through a metal associate protic oxonium ylide intermediate as shown in Scheme 2: co-ordination of *p*-methoxyphenyl diazoacetate with $InBr_3$ gives the intermediate **I**. Loss of N_2 may occur to form a vinyl cationic intermediate **II**.[4a] Reaction of the electrophilic intermediate **II** with BnOH may result in the metal associate protic oxonium ylide intermediate **III**, which undergoes a proton transfer to give the O–H insertion product **9a**. An electron-donating substitution on the phenyl ring of the diazo compound should help to stabilize the vinyl cationic intermediate **IIa**. Based on the assumption of the oxonium ylide formation, we envisioned that the protic oxonium intermediate **III** could be trapped by an electrophile, such as a carbonyl compound to give **IV**, which leads to the corresponding three-component product via a 'delayed proton transfer' process (Scheme 2).

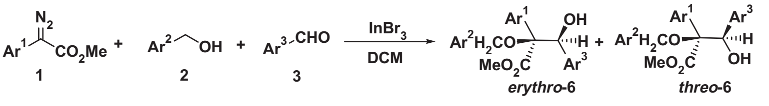
Initially, *p*-NO_2 benzaldehyde (**3a**) was selected to verify our hypothesis. *para*-Methoxyphenyl diazoacetate **1a** was added to a mixture of benzyl alcohol **2a** and **3a** in the presence of $InBr_3$. Gratifyingly, the reaction gave excellent yield (95%) and high diastereoselectivity (96:4) favoring *erythro* isomer (Table 1, entry 2). In contrast, the same reaction catalyzed by $Rh_2(OAc)_4$ alone gave the same product in low dr (62:38) (Table 1, entry 1). Inspired by such a promising result, the reaction was extended to additional substrates and representative results are summarized in Table 1. Similarly high dr (95:5) was obtained when using phenyl diazoacetate (**1b**) and *p*-methylphenyl diazoacetate (**1c**) as substrates, whereas product yields are little lower (entries 3 and 4). The



Scheme 2. Proposed diazo decomposition pathways catalyzed by $InBr_3$.

Table 1

Three-component reactions of an aryldiazoacetate, an alcohol and an electron-deficient aldehyde[a]



Entry	Ar^1	Ar^2	Ar^3	**6**	$InBr_3$	
					Yield %[d]	Dr(*erythro*:*threo*)[e]
1[b,c]	*p*-OMe Ph	Ph	*p*-NO_2 Ph	**6a**	87	62:38
2	*P*OMePh	Ph	*p*-NO_2Ph	**6a**	95	96:4
3	Ph	Ph	*p*-NO_2Ph	**6b**	52	95:5
4	*p*-CH_3Ph	Ph	*p*-NO_2Ph	**6c**	62	95:5
5	*p*-OMePh	Ph	*o*-NO_2Ph	**6d**	73	90:10
6	*p*-OMePh	Ph	*p*-CF_3Ph	**6e**	50	96:4
7	*p*-OMePh	*p*-ClPh	*p*-NO_2Ph	**6f**	75	96:4
8	*p*-OMePh	*p*-CH_3Ph	*p*-NO_2Ph	**6g**	69	95:5

[a] All reactions were carried out in CH_2Cl_2 at 40 °C for 4 h with 1:2:3 = 1.5:1.5:1.0 (mmol) by using 20 mol % $InBr_3$.

[b] Reaction was carried out in CH_2Cl_2 at 40 °C for 1 h with 1:2:3 = 1.0:1.1:1.1 (mmol) by using 1 mol % $Rh_2(OAc)_4$.

[c] Isolated yield of both isomers after column chromatography purification.

[d] Isolated yield of *erythro*-isomer after column chromatography purification.

[e] Determined by ^1H NMR of unpurified reaction mixtures.

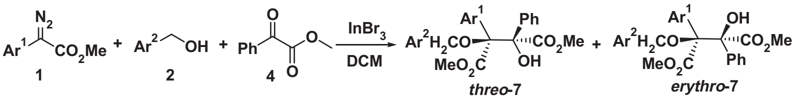
reaction proceeded well with electron deficient aromatic aldehydes due to enhanced electrophilicity of the aldehydes that enable them to efficiently trap the protic oxonium intermediate (entries 2–8). When using electron rich *para*-methoxyl benzaldehyde as a substrate, corresponding trapping product was obtained in only a 22% yield with 50:50 dr.

The $InBr_3$ catalyzed three-component reaction was further extended to other electron deficient carbonyl compounds. The reaction proceeded smoothly with aryl keto esters and isatins, and the results are summarized in Tables 2 and 3, respectively. In the case of using aryl keto esters, $InBr_3$ gave higher dr than copper catalyst. While $CuPF_6(CH_3CN)_4$ gave the product in very low dr (51:49) (Table 2, entry 1), dr of greater than 80:20 was observed when using $InBr_3$ as the catalyst (Tale 2, entries 2–6). The more electron rich diazo compounds gave both higher yield and dr Table 2, entries 2–4). Significant effect of the substitution of benzyl alcohol on the reaction outcome was observed in this case, as electron rich *p*-methylbenzyl alcohol gave both decreased yield and dr (Table 2, entry 6 versus entries 2 and 5). Istains were identified as good substrates as well. While $Rh_2(OAc)_4$ gave the reaction with good yield and excellent dr (99:1) favoring *erythro* isomer (Table 3, entry 1), the diastereoselectivity was switched to *threo* when using the $InBr_3$ catalyst (Table 3, entries 2–5). The $InBr_3$ catalyzed three-component reactions with isatins gave good yield with moderate to high dr favoring *threo* isomer.

Several control experiments were carried out to exclude the possibility that the three-component products **6** or **7** were formed from the O–H insertion product **9a** via a stepwise reaction pathway. The reaction of **9a** with **3a** or **4a** did not provide any three-component product **6a** or **7a** in the presence of $InBr_3$. Treatment of diazo compound **1a** and aldehyde **3a** in the presence of $InBr_3$ afforded only dimerization product of the diazo compound (Scheme 3). The control experiments indicate that the three-component reaction only occurs when the all three substrates are concurrent, and are in agreement with the proposed reaction pathway shown in Scheme 2.

In conclusion, we first report $InBr_3$ catalyzed three-component reactions of aryldiazoacetates, alcohols and carbonyl compounds to afford α,β-dihydroxyl acid derivatives in an efficient and cost effective way. $InBr_3$ acts as a Lewis acid to decompose a diazo compound in generating a protic oxonium ylide intermediate, which is trapped by an electron deficient carbonyl compound in a highly diastereoselective manner. The reactions still have some limitations in substrate scope. Further work will emphasize on expanding the substrate scope and managing enantioselective control.

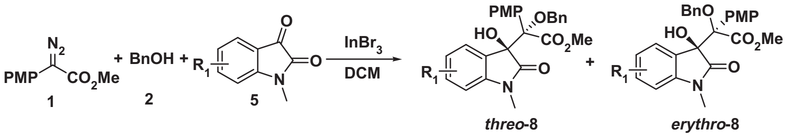
Table 2
Three-component reactions of an aryldiazoacetate, an alcohol, and a ketoester[a]



Entry	Ar^1	Ar^2	**7**	InBr$_3$	
				Yield %[d]	Dr(*threo: erythro*)[e]
1[b,c]	Ph	Ph	**7c**	68	41:59
2	*p*-OMePh	Ph	**7a**	62	95:5
3	*p*-CH_3Ph	Ph	**7b**	55	90:10
4	Ph	Ph	**7c**	26	86:14
5	*p*-OMePh	*p*-ClPh	**7d**	63	92:8
6	*p*-OMePh	*p*-CH_3Ph	**7e**	34	80:20

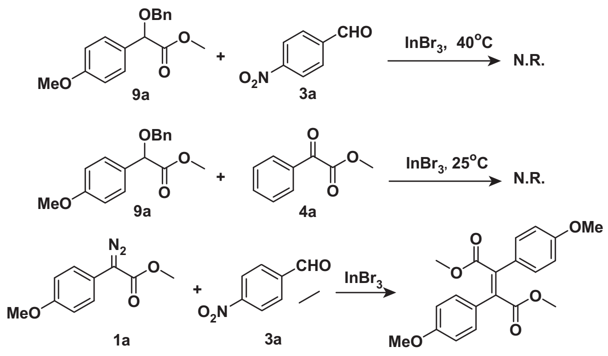
[a] All reactions were carried out in CH_2Cl_2 at 25 °C for 4 h with 1:2:4 = 1.2:1.2:1.0 (mmol) by using 20 mol % $InBr_3$.
[b] Reactions were carried out in CH_2Cl_2 at 40 °C for 2 h with 1:2:3 = 1.0:1.2:1.2 (mmol) by using 10 mol % $CuPF_6(CH_3CN)_4$.
[c] Isolated yield of both isomers after column chromatography purification.
[d] Isolated yields of *threo*-isomer after column chromatography purification.
[e] Determined by ^{1}H NMR of unpurified reaction mixtures.

Table 3
Three-component reactions of an aryldiazoacetate, an alcohol, and an isatin[a]



Entry	R^1	**8**	InBr$_3$	
			Yield %[c]	Dr(*threo:erythro*)[d]
1[b]	H	**8a**	80	1:99
2	H	**8a**	90	90:10
3	4-Cl	**8b**	84	68:32
4	5-Cl	**8c**	56	62:38
5	6-Cl	**8d**	67	69:31

[a] All reactions were carried out in CH_2Cl_2 at 40 °C for 4 h with 1:2:5 = 2.0:2.0:1.0 (mmol) by using 40 mol % $InBr_3$.
[b] Reaction was carried out in CH_2Cl_2 at 40 °C for 1 h with 1:2:3 = 1.2:1.5:1.0 (mmol) by using 1 mol % $Rh_2(OAc)_4$.
[c] Isolated yields of *threo* and *erythro*-isomers after column chromatography purification.
[d] Determined by ^{1}H NMR of unpurified reaction mixtures.



Scheme 3. Control reactions.

Acknowledgments

We wish to thank the National Science Foundation of China (20932003, 21002033) and the MOST of China (2011CB808600) for financial support and Shanghai (09JC1404901, 10XD1401700) for sponsorship.

Supplementary data

Supplementary data (complete experimental details and spectroscopic characterization of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.005.

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