Synthetic Method for the Preparation of 2-Aminomethyl-1,3-diene Derivatives through Indium-Mediated 1,3-Butadien-2-ylation of Imines

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ABSTRACT



An efficient method for the preparation of a variety of 2-aminomethyl-1,3-dienes was developed through the reaction of imines with organoindium reagent generated in situ from indium and 1,3-dibromo-2-butyne. Three-component reactions of aldehydes, amines, and organoindium reagents gave successful results in a one-pot process.

Carbon-carbon bond formation by nucleophilic addition of carbon nucleophiles to imines is an important tool for synthesizing complex biologically active nitrogen-containing compounds.¹ While addition of a variety of carbon nucleophiles to carbonyl compounds has been extensively investigated and well established, considerably less successful

10.1021/ol9005213 CCC: \$40.75 © 2009 American Chemical Society Published on Web 05/07/2009 results were obtained in the analogous reactions with imines. The major problems are the relatively low reactivity of unactivated imines toward nucleophilic addition and deprotonation of imines derived from enolizable carbonyl compounds to form enamines. During the last decades, a variety of carbon nucleophiles have been used in the addition reaction of imines.² However, the preparation of 2-aminomethyl-1,3-diene derivatives through an addition reaction of

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the 1,3-butadien-2-yl moiety to imines is still rare in organic reactions. Of these, the Grignard cross-coupling reaction of 2-bromo-3-aminopropene with vinyl bromides suffers from poor chemoselectivity.³ 2-Halomethyl-1,3-dienes, though quite effective in reacting with secondary amines to give 2-aminomethyl-1,3-dienes, are not convenient to prepare.^{3b,4} Although 2-aminomethyl-1,3-dienes have been produced by the reaction of 2 equiv of allene with various amines in the presence of Pd catalysts, bis(dienyl)amines as a side product were contaminated.⁵ Enyne cross metathesis is a good syntheic method of 2-N-arylmethyl-1,3-butadienes.⁶ Because so much is now known about the Diels-Alder reaction,⁷ we were convinced that when we found an efficient addition reaction of the 1,3-butadien-2-yl group to imines, then this reaction would prove useful to synthetic organic chemists for the synthesis of a variety of 2-aminomethyl-1,3-diene derivatives as well as six-membered carbocycles. Herein, we report indium-mediated addition reactions of 1,3-dien-2-yl indium generated in situ from 1,4-dibromo-2-butyne and indium with imines or the mixture of aldehyde and amine for the synthesis of 2-aminomethyl-1,3-diene derivatives (Scheme 1).



We initially examined the addition reactions of an organoindium reagent⁸ generated in situ from indium and 1,4-dibromo-2-butyne $(2)^9$ with imine (1d). The results are summarized in Table 1. The reaction of 1d with 3 equiv of indium and 1.5 equiv of 2 in THF, DMF, and dioxane did not proceed (entries 1-3). The use of H₂O gave the desired product 3d in 17% yield through 1,3butadien-3-ylation to 1d. Compound 4d was additionally obtained in 42% yield from benzaldehyde derived from hydrolysis of imine (entry 4).¹⁰ Although the model reaction produced 3d in 32% yield in MeOH, formation of 4d (30%) was unavoidable (entry 6). Therefore, we added drying agents such as 4 Å molecular sieves and MgSO₄ to suppress the hydrolysis of imine 1d (entries 7 and 8). In the case of MgSO₄, the yield (47%) of 3d was increased by 15% (entry 6 vs 8), and formation of 4d was suppressed (entry 8). EtOH was the best solvent among several reaction media examined (THF, DMF, dioxane, H₂O, H₂O-THF, MeOH, and EtOH) (entries 1-9). The present reaction was carried out with 1 equiv of MgSO₄ in EtOH, producing the desired product 3d in 70% yield together with 4d in 21% yield (entry 9). With this result in hand, the stoichiometry of indium and 2 was investigated in detail (entries 10-13). Of the addition reactions examined, the best results were obtained with 2 equiv of indium and 1.5 equiv of 2 in the presence of 1 equiv of MgSO₄ at 25 °C for 2 h in EtOH under a nitrogen atmosphere, affording 3d selectively in 86% yield (entry Table 1. Optimization of 1,3-Butadien-2-ylation to Imine 1d with Indium and ${\bf 2}$

				PhHŅ		
	Ph N ^F	^{Ph} +	Br rt	► Ph	\checkmark	
	1d	2	<u>.</u>	3d		
			ln	2	time	yield
entry	solvent	$\operatorname{additive}^{a}$	(equiv)	(equiv)	(h)	$(\%)^b$
1	THF		3.0	1.5	20	0
2	DMF		3.0	1.5	20	0
3	Dioxane		3.0	1.5	20	0
4	H_2O		3.0	1.5	3	17(42)
5	H_2O -THF ^c		3.0	1.5	3	15(38)
6	MeOH		3.0	1.5	3	32(30)
7	MeOH	MS-4 Å	3.0	1.5	2	37(25)
8	MeOH	$MgSO_4$	3.0	1.5	2	47(19)
9	EtOH	$MgSO_4$	3.0	1.5	2	70(21)
10	EtOH	$MgSO_4$	2.0	1.0	5	54(21)
11	EtOH	$MgSO_4$	1.3	1.0	5	42(19)
12	EtOH	$MgSO_4$	2.0	1.5	2	86(5)
13	EtOH	$MgSO_4$	2.7	2.0	2	73(18)
14	EtOH	$MgSO_4 - InCl_3^d$	2.0	1.5	2	50(38)
15	EtOH	$MgSO_4$ - $AcOH^e$	2.0	1.5	1	55(15)
16	EtOH	Na_2SO_4	2.0	1.5	1	75(14)
a 1	aquin of Ma	SO or No SO III	as used b	Number	in nor	anthaca

^{*a*} 1 equiv of MgSO₄ or Na₂SO₄ was used. ^{*b*} Numbers in parentheses indicate yield of **4d**. ^{*c*} H₂O:THF = 3:1. ^{*d*} 20 mol % of InCl₃ was used. ^{*e*} 6 equiv of AcOH was used.

12). The use of indium in less than 2 equiv and **2** in less than 1.5 equiv resulted in a sluggish reaction and gave lower yields even at longer reaction times (entries 10 and 11). The use of MgSO₄–InCl₃ and MgSO₄–AcOH as an additive gave the desired product **3d** in 50% and 55% yields together with **4d** in 38% and 15% yields, respectively (entries 14 and 15). There are no **6**, **7**, and **5d** formed in these reactions. The ¹H and ¹³C NMR spectra of **3d** are consistent with benzylphenylamine possessing the 1,3-dien-2-yl group. The four sp^2 resonances (100 MHz) of the 1,3-dien-2-yl group appeared at 145.4, 136.8, 117.8, and 115.1 ppm, indicating that compound **3d** was selectively produced.



To demonstrate the scope and limitation of the present method, we applied this reaction system to a variety of imine compounds, affording 2-aminomethyl-1,3-diene derivatives (Table 2). Under the optimized conditions, imine **1a** gave the 1,3-diene **3a** and allenylmethylamine **5a** in 61% and 5% yields, respectively (entry 1). Treatment of **1b** with indium

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Table 2. Selective 1,3-Butadien-2-ylation to Imines^a

R ¹	<>N ⁻ R ²	+	∖ + In − Br	EtOH MgSO₄	$R^{2}HN$	¥#
	1	2		0 1	3	<u> </u>
				time		yield
entry	imine	\mathbb{R}^1	\mathbb{R}^2	(h)	product	(%)
1	1a	<i>i</i> -Pr	Ph	4	3a	$61(5)^{b}$
2	1b	$C_{6}H_{11}$	Ph	7	3b	$60(4)^{c}$
3	1c	PhCH=CH	Ph	5	3c	51
4	1d	Ph	Ph	2	3d	$86(5)^{c}$
5	1e	4-Cl-C ₆ H ₄	Ph	2	3e	$75(8)^{b}$
6	1f	$3-Br-C_6H_4$	Ph	3	3f	$60(9)^{c}$
7^d	1g	$2\text{-I-C}_6\text{H}_4$	Ph	5	3g	$61(19)^{c}$
8	1h	$4\text{-Me-C}_6\text{H}_4$	Ph	2	3h	$72(7)^{b}$
9	1i	$2\text{-Me-C}_6\text{H}_4$	Ph	4	3i	$67(4)^{b}$
10^e	1j	$3-HO-C_6H_4$	Ph	2	3j	$75(5)^{b}$
11	1k	$4-MeO_2C-C_6H_4$	Ph	1	3k	$65(13)^{b}$
12	1l	2-Furyl	Ph	2	31	$67(4)^{c}$
13	1m	Ph	$4\text{-I-C}_6\text{H}_4$	1	3m	$74(14)^{c}$
14	1n	Ph	$4-MeO-C_6H_4$	4	3n	$76(11)^{c}$
15	10	Ph	Bn	6	30	$62(17)^{c}$
16^e	1p	EtO_2C	BnO	6	3p	$77(8)^{c}$
17^e	1q	$\mathrm{EtO}_{2}\mathrm{C}$	$4-MeO-C_6H_4$	6	3q	$65(9)^{c}$

^{*a*} Reactions were carried out with 1 equiv of **1**, 1.5 equiv of **2**, and 2 equiv of indium in the presence of 1 equiv of MgSO₄ at rt. ^{*b*} **5** Derivatives. ^{*c*} **4** Derivatives. ^{*d*} Indium: **2** = 3:2.3. ^{*e*} 3 equiv of indium was used.

and 2 in the presence of MgSO₄ produced the desired product (3b) in 60% yield (entry 2). In the case of imine-derived trans-cinnamaldehyde, 1,3-diene 3c was obtained in 51% yield (entry 3). The presence of either an electron-donating or electron-withdrawing group, such as chloride, bromide, iodide, methyl, hydroxyl, and methoxy-carbonyl groups, on the aromatic ring had little effect on the efficiency and selectivity of indium-mediated 1,3-butadien-2-ylation of imine (entries 5-11). Treatment of imine **1e** and **1f** with organoindium reagent in the presence of MgSO₄ gave the 1,3-dienes (**3e** and **3f**) in 75% and 60% yields, respectively (entries 5 and 6). Imine 1g reacted with 3 equiv of indium and 2.3 equiv of 2 to provide 1,3-diene 3g in 61% yield (entry 7). 1,3-Butadien-2-yl indium smoothly added to imines 1h and 1i to produce 1,3-dienes 3h and 3i in 72 and 67% yields, respectively (entries 8 and 9). It is noteworthy that protection of a hydroxyl group on substrates is not necessary as demonstrated by the reaction of imine 1j (entry 10). Imine 1k bearing a 4-methoxycarbonyl group turned out to be compatible with the present reaction conditions (entry 11). 2-Furfural worked equally well with the employed reaction conditions, producing the 1,3-diene **31** in 67% yield (entry 12). Altering the electron demand of the substituents on the aryl rings of anilines produced the 2-aminomethyl-1,3-dienes in good yields together with 1,3-butadien-2-yl methanols in about 10% yields (entries 13-15). Subjecting imines 1m and 1n to the organoindium reagent resulted in 3m and 3n in 74% and 76% yields, respectively (entries 13 and 14). Reaction of glyoxylic oxime ether **1p** and glyoxylic imine 1q with 3 equiv of indium and 1.5 equiv of 2 provided *N*-protected α -amino esters **3p** and **3q** having the 1,3-diene group in 77% and 65% yields, respectively (entries 16 and 17).

With this result in hand, three component reactions of aldehydes, amines, and organoindium reagents were investigated in a one-pot process (Table 3). The three component

Table 3. 1,3-Butadien-2-ylation Using Aldehydes, Amines, and Organoindium Reagents in One Pot^{a}

R ¹ CH0	D + R ² NH ₂ +	Br 2	∖ Br + In –	additive EtOH	R ₂ HN R ¹	
				time		yield
Entry	\mathbb{R}^1	\mathbb{R}^2	additive	(h)	product	$(\%)^{g}$
1	Ph	Phb	$MgSO_4$	3	3d	50(18)
2	Ph	Ph^{b}	MgSO ₄ -InCl ₃ ^c	3	3d	60(12)
3	Ph	Ph^b	$MgSO_4^d$	3	3d	40(23)
4	Ph	Ph^b	MS-4 Å	3	3d	54(18)
5	Ph	Ph	AcOH	2	3d	64(8)
6	Ph	Ph	$AcOH^e$	2	3d	49(20)
7	Ph	Ph	AcOHf	2	3d	63(9)
8	$C_{6}H_{11}$	Ph	AcOH	6	3b	48(23)
9	Ph	$4-MeO-C_6H_4$	AcOH	6	3n	56(19)
10	$4-Cl-C_6H_4$	Ph	AcOH	5	3e	65(10)
11	$3-HO-C_6H_4$	Ph	AcOH	5	3j	59(12)
12	$4-MeO_2C-C_6H_4$	Ph	AcOH	1	3k	58(18)

^{*a*} Reactions were carried out with 1 equiv of aldehydes, 1.5 equiv of amines, 1.5 equiv of **2**, and 2 equiv of indium in the presence of 1 equiv of MgSO₄ or 1 equiv of AcOH at rt. ^{*b*} 1 equiv of amine was used. ^{*c*} 20 mol % InCl₃ was used. ^{*d*} 3 equiv of MgSO₄ wasused. ^{*e*} 0.5 equiv of AcOH was used. ^{*f*} 2 equiv of AcOH was used. ^{*s*} Numbers in parentheses indicate yields of **4**.

reaction of benzaldehyde, aniline, and organoindium reagent in situ generated from 2 equiv of indium and 1.5 equiv of 1,4-dibromo-2-butyne (2) in the presence of 1 equiv of MgSO₄ has been carried out at 25 °C for 3 h in EtOH under a nitrogen atmosphere, affording selectively the desired product 3d (50%) together with 4d (18%) (entry 1). A variety of additives, such as MgSO₄, MgSO₄–InCl₃, 4 Å molecular sieves, and AcOH, were examined to increase the product yield as well as suppress 4d. Of the additives examined, 1 equiv of AcOH gave the best result (entry 5). Under the optimum conditions, the desired product 3d was produced in 64% yield. Treatment of cyclohexanecarbaldehyde and aniline with indium and 2 afforded 3b in 48% yield in a one-pot process (entry 8). In situ generated imine **1n** was readily 1,3-butadien-2-ylated with organoindium reagent to provide **3n** in 56% yield (entry 9). We were pleased to obtain **3e** and **3j** in 65% and 59% yields, respectively, from three component reactions in a one-pot process (entries 10 and 11). In the case of methyl 4-formylbenzoate, the desired product 3k was produced in 58% yield together with 4k in 18% yield (entry 12). Although treatment of indium and 2 with a mixture of aldehydes and amines gave an inferior result in terms of the chemical yields, the present method efficiently assembled three components in a one-pot process, producing the 2-aminomethyl-1,3-diene derivatives in good vield.

In summary, we have developed a convenient protocol for the synthesis of a variety of 2-aminomethyl 1,3-diene derivatives through the reactions of imines with organoindium reagents generated in situ from indium and 1,3dibromo-2-butyne. Three component reactions of aldehydes, amines, and organoindium reagents gave successful results in a one-pot process.

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Supporting Information Available: Experimental procedure and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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