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Rhodium-catalyzed approach to Mannich-type products using aldimine, α,β-unsaturated ester, and hydrosilane†

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Received (in Cambridge, UK) 20th March 2002, Accepted 1st May 2002
First published as an Advance Article on the web 16th May 2002

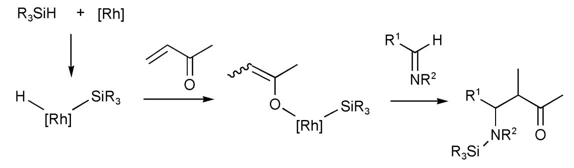
A rhodium-catalyzed method for the synthesis of β-amino esters was accomplished in a one-pot procedure from aldimine, α,β-unsaturated ester and hydrosilane.

Mannich-type reactions of an aldimine with an enolate component are some of the most important and versatile tools to construct β-amino carbonyl compounds. These reactions provide useful routes for the synthesis of β-amino esters which are useful as the immediate precursors of β-lactams and β-amino acids.[1] Recent patterns of these reactions are categorized as the combination of aldimines and enoxysilanes with the assistance of some types of Lewis acid,[2,3] though some exceptions have been reported.[4] The advantages for the use of enoxysilanes as a nucleophile are widely accepted, however, some troublesome procedures are required for their isolation in sufficient purity.[5]

On the other hand, the transition-metal-catalyzed carbon–carbon bond forming reaction is regarded as one of the most convenient and facile tools for constructing a designed molecule in the past decades.[6] In particular, it is fascinating that several bonds are formed in an orderly manner in a one-pot reaction of more than three starting substrates under almost neutral conditions.[7] We have found that some types of rhodium complex enable multi-component couplings including a hydrosilane as a starting component.[8] In these reactions, some have indicated that rhodium enolate plays an important role as a key intermediate in these multi-component couplings. The formation of a rhodium enolate is elucidated by the insertion of an α,β-unsaturated carbonyl compound into the Rh–H bond generated by the oxidative addition of a hydrosilane to a low valent rhodium metal. The resultant enolate possesses sufficient nucleophilicity to attack an appropriate electrophile.[8a,b,o] Along this line, we attempted to design a facile route to β-amino esters (Scheme 1). We report herein a rhodium-catalyzed method to give a Mannich-type product from the reaction of an aldimine with an α,β-unsaturated ester and a hydrosilane.

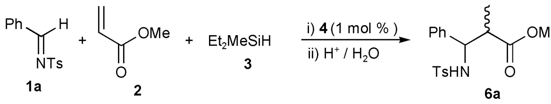
First of all, a CH_2Cl_2 solution containing aldimine **1a**, methyl acrylate (**2**), diethylmethylsilane (**3**), and 1 mol% of $[Rh(cod)(PPh_3)_2]OTf$ (**4a**, cod = cycloocta-1,5-diene) was heated for 5 h at 45 °C to afford the *N*-diethylmethylsilyl-β-amino ester, **5a**, corresponding to **6a**. Protodesilylation of **5a** in acidic aqueous EtOH afforded the β-amino ester **6a** in 81% yield as a mixture of two diastereomers (*syn*:*anti* = 46:54, entry 1 in Table 1). The structure of **6a** was assigned on the basis of its ^{1}H and ^{13}C NMR, IR, and combustion analysis. This three-component coupling of **1a**, **2**, and **3** proceeded incompletely even in the presence of 1 mol% of **4a** when the reaction was conducted for 24 h at 25 °C (entry 2 in Table 1). In addition to **6a** (31%), $TsNH_2$ was obtained in 40% yield after chromatographic purification of the crude mixture. Since an aldimine **1a** is immediately hydrolyzed in aqueous EtOH to afford $TsNH_2$ and benzaldehyde, the concomitant formation of $TsNH_2$ reflects the relative quantity of aldimine **1a** remaining intact under the given reaction conditions. A neutral and zero-valent rhodium complex, $Rh_4(CO)_{12}$ (**4b**), also showed a similar catalytic efficiency for this Mannich-type reaction, though more vigorous conditions were required for the complete conversion of **1a** (entry 3 in Table 1). The yield of **6a** increased dramatically in the reaction catalyzed by $[Rh(cod)\{P(OPh)_3\}_2]OTf$ (**4c**) under conditions similar to the reaction using **4a** (entry 5 in Table 1). The solvent used for this reaction significantly affected both the rate and the product yield (entries 5, 7, and 8 in Table 1). These results suggest that CH_2Cl_2 is the solvent of choice in the reactions using **4c** as the catalyst precursor. In contrast, this coupling reaction gave a sluggish result when a mixture of $[Rh(dppe)Cl]_2$ and AgOTf (**4d**, dppe = 1,2-bis(diphenylphosphino)ethane) was used as a catalyst precursor instead of **4c** (entry 9 in Table 1). Thus, it is deduced that the best result for this Mannich-type transformation is obtained by the combination of **4c** as the catalyst precursor and CH_2Cl_2 as the solvent.

On the basis of the preliminary information, several types of aldimines (**1**) were subjected to the present three-component coupling in the presence of 1 mol% of the rhodium(I) catalyst. Selected results are summarized in Table 2. The reactivity of **1** for this reaction was significantly affected by the structure and electronic properties of both R^1 and R^2. The 4-methylbenzenesulfonyl group on the imino-nitrogen showed a remarkable influence on increasing the yield of **6** in comparison with the



Scheme 1

Table 1 Rhodium-catalyzed Mannich-type reaction of aldimine **1a** with **2** and **3**[a]



Entry	Catalyst precursor[b]	Solvent	Conditions °C/h	Yield of **6a**[cd] (*syn*:*anti*)	$TsNH_2$ (%)[e]
1	**4a**	CH_2Cl_2	45/5	81 (46:54)	—
2	**4a**	CH_2Cl_2	25/24	31 (48:52)	40
3	**4b**	C_6H_6	85/88	82 (65:35)	—
4	**4b**	C_6H_6	25/24	40 (53:47)	49
5	**4c**	CH_2Cl_2	45/6	96 (32:68)	—
6	**4c**	CH_2Cl_2	25/21	69 (44:56)	—
7	**4c**	THF	70/28	78 (39:61)	—
8	**4c**	C_6H_6	85/69	92 (47:53)	—
9	**4d**	CH_2Cl_2	25/24	28 (60:40)	27

[a] A mixture of **1a** (1 mmol), **2a** (2 mmol) and **3** (2 mmol) in 2 ml of solvent was added to a solution (4 ml) of **4** (1 mol% for **1a**) and the resulting mixture was then stirred under the conditions shown above. [b] **4a**: $Rh(cod)(PPh_3)_2]OTf$, **4b**: $Rh_4(CO)_{12}$, **4c**: $[Rh(cod)\{P(OPh)_3\}_2]OTf$, **4d**: $[Rh(dppe)Cl]_2$ + 2 AgOTf. [c] The ratio of the two diastereoisomers was determined by ^{1}H NMR analysis. [d] Isolated yield. [e] The yield of recovered $TsNH_2$ after chromatographic purification.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b2/b202773a/

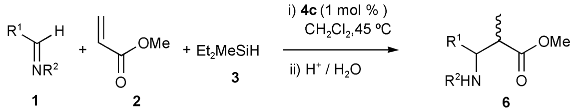
DOI: 10.1039/b202773a

other aldimines derived from benzaldehyde (Table 1 and entries 1–5 in Table 2). β-Amino esters (**6b–e**) were obtained in modest yields from the corresponding aldimine (entries 2–5 in Table 2). *N*-Benzyl-*N*-2-methoxyphenylamine (**7e**, 15% based on the starting **1e**) was isolated in addition to the expected product **6e** (60%) when **1e** was reacted with **2** and **3** even in the presence of the less active catalyst, **4a** (entry 5 in Table 2). The formation of **7e** suggests that there is another path catalyzed by **4**, *i.e.*, hydrosilylation, to consume **1e** in a one-pot reaction of **1e**, **2** and **3**. Furthermore, a similar three-component coupling was tested using several aldimines derived from the condensation between $TsNH_2$ and other aldehydes (entries 6–10 in Table 2). The presence of a methoxy group at the *ortho*-position on the phenyl ring of R^1 affects the reaction rate to form **6**. The reaction of *N*-(2-methoxybenzylidene)-4-methylbenzenesulfonamide (**1h**) completed within 4 h afforded the corresponding β-amino ester (**6h**) in 93% yield (entry 8 in Table 2). A similar effect was expected when an aldimine possessing an *ortho*-hydroxy group on the phenyl ring of R^1 is employed in place of **1h**, though a longer reaction time was required for the complete consumption of **1i** (entry 9 in Table 2). It is noteworthy that nucleophilic attack on **1j** selectively proceeds in a 1,2-fashion to give **6j** in 56% yield (entry 10 in Table 2). In contrast to these observations, the corresponding **6** was not obtained at all in the reaction of an aldimine bearing an aliphatic substituent on the imino-nitrogen. For example, *N*-cyclohexyl aldimine **1k** could not be converted into the β-amino esters under similar reaction conditions, but **1k** remained intact (entry 11 in Table 2).

In all the examples presented here, the reaction path was generally controlled to afford a β-amino ester, whereas the diastereoselectivity of the products is moderate and both diastereomers are inseparable through column chromatography at this stage (Table 1 and 2). Although numerous examples of the Mannich-type reaction for aldimines with enoxysilanes are reported, the general procedure for controlling the diastereochemistry has not been established.[3] Therefore, the present three-component coupling retains a sufficient usefulness in synthetic organic chemistry despite this defect. It discloses a new route to design certain types of β-amino carbonyl compounds under almost neutral conditions.

In summary, a useful method for the synthesis of β-amino esters has been developed. This methodology provides a convenient route for Mannich-type transformation of the aldimines with an α,β-unsaturated ester and a hydrosilane in the catalysis of a cationic rhodium(I) complex. In this reaction, the rhodium enolate plays an important role in the nucleophilic attack on the sp^2 carbon of the aldimine. Since only a few examples have been reported for Mannich-type transformation catalyzed by a transition metal complex,[9] this article describes good examples for the application of transition metals as catalysts of Mannich-type reactions.

Table 2 Rhodium-catalyzed Mannich-type reaction of aldimine **1** with **2** and **3**[a]



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Entry		R^1	R^2	Time/h	Product (%)[b]	*syn*:*anti*[c]
1	**1a**	Ph	*p*-Ts	6	**6a** (96)	32:68
2	**1b**	Ph	*p*-ClC_6H_4	20	**6b** (87)	51:49
3	**1c**	Ph	Ph	27	**6c** (82)	54:46
4	**1d**	Ph	*p*-$MeOC_6H_4$	15	**6d** (71)	51:49
5	**1e**	Ph	*o*-$MeOC_6H_4$	4	**6e** (60)[de]	42:58
6	**1f**	*p*-ClC_6H_4	*p*-Ts	5	**6f** (76)	29:71
7	**1g**	*p*-$MeOC_6H_4$	*p*-Ts	30	**6g** (95)[e]	41:59
8	**1h**	*o*-$MeOC_6H_4$	*p*-Ts	4	**6h** (93)	50:50
9	**1i**	*o*-HOC_6H_4	*p*-Ts	8	**6i** (75)	38:62
10	**1j**	(*E*)-PhCH=CH	*p*-Ts	48	**6j** (56)[f]	37:63
11	**1k**	Ph	Cyclohexyl	24	**6k** (0)	—

[a] A mixture of **1** (1 mmol), **2** (2 mmol) and **3** (2 mmol) in 2 ml of solvent was added to a 4 ml solution of **4c** (1 mol% for **1**) and the resulting mixture was then refluxed for the period shown above. [b] Isolated yield. [c] The ratio of the two diastereoisomers was determined by ^1H NMR analysis. [d] Another product, *N*-benzyl-*N*-2-methoxyphenylamine (**7e**), was concomitantly obtained in 15% yield with **6e**. [e] **4a** was used for catalyst precursor instead of **4c**. [f] $TsNH_2$ was recovered in 32% yield.

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