Tetrahedron Letters 53 (2012) 4721-4724

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Trifluoroacetic anhydride—catalyzed conjugate addition of boronic acids to α , β -unsaturated ketones

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ARTICLE INFO

Article history: Received 11 May 2012 Revised 18 June 2012 Accepted 22 June 2012 Available online 2 July 2012

Keywords: Conjugate addition Boronic acids α,β-Unsaturated ketone Acid anhydride Catalysis

ABSTRACT

The conjugate addition of boronic acids to α,β -unsaturated ketones catalyzed by acylating reagents has been explored. The results show that trifluoroacetic anhydride catalyzes the addition of vinylboronic acids under experimentally simple and metal-free conditions for a variety of substrates with good yields. © 2012 Elsevier Ltd. All rights reserved.

The formation of C–C bonds is pivotal in the building of complex organic molecules. The development of new synthetic procedures which enable the selective formation of this type of linkage under mild reaction conditions is an area of active research. Among these methods, the conjugate addition reaction of carbon nucleophiles to electron-deficient alkenes has become one of the most important.¹

In particular, the conjugate addition reaction of boronic acids to a wide variety of electron-deficient systems under transition-metal catalysis constitutes a useful synthetic method. Most boronic acids are terminally stable compounds, resistant to air and humidity, compatible with many functional groups readily attacked by conventional organometallic reagents, and have low toxicity. In addition, a large number of them are nowadays commercially available, and can also be prepared by various synthetic routes.² However, the direct conjugate addition of boronic acids is precluded by their low nucleophilicity, and some kind of activation is normally required. This can be achieved by transmetalation to transition metals, mainly Rh and Pd, in catalytic cycles.^{3,4} Although less developed, this type of reaction can also be promoted by organic molecules, either stoichiometrically⁵ or catalytically.⁶

In the search for new reagents that allow the activation of boronic acids catalytically toward the conjugate addition to simple α , β unsaturated ketones under metal-free mild reaction conditions, we have focussed our attention on acylation reagents. The interaction of boronic acids with this type of reagents (Scheme 1) leads to the

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Scheme 1. Activation of boronic acids toward conjugate addition.

in situ formation of mono or diacylboronates **A**, where the Lewis acidity of the boron atom is enhanced with respect to the starting boronic acid.⁷ This may permit coordination of boron to the lone electron-pair of the carbonyl oxygen, thus facilitating the transfer of the nucleophilic carbon backbone in an intramolecular fashion.⁸

We began our research by exploring different acylation reagents in the conjugate addition of chalcone **2a** with 2-phenylvinylboronic acid **1a**. These results are gathered in Table 1.

We observed that reaction in the presence of Ac₂O, either in catalytic or stoichiometric amounts (Table 1, entries 1 and 2), led to the formation of the conjugate addition product **3a** in a low yield. However, the use of Ac₂O as the solvent at 60 °C permitted the synthesis of **3a** in a higher yield (Table 1, entry 3). When the reaction was carried out using AcCl as the promoter, we observed again a



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Table 1

Conjugate addition of chalcone (2a) with 2-phenylvinylboronic acid (1a)^a



Entry	RCOX (equiv)	T (°C)	3a ^b (%)
1	Ac ₂ O (0.2)	25	10
2	Ac ₂ O (1.0)	25	25
3	Ac ₂ O ^c	60	40
4	AcCl (1.0)	25	40
5	AcCl ^c	25	90
6	(CF ₃ CO) ₂ O (0.2)	25	95

 a 1a (0.36 mmol), 2a (0.24 mmol), CH_2Cl_2 (0.4 mL), RCOX (72 $\mu mol,$ 0.3 equiv), 18 h.

^b Isolated yield.

Table 2

^c Reactions carried out with Ac₂O or AcCl as solvent (1.0 mL/mmol).

Trifluoroacetic anhydride-catalyzed conjugate addition of 2 with 1^a

low yield under stoichiometric conditions (Table 1, entry 4), but the conversion was high when AcCl was used as the solvent, even at rt (Table 1, entry 5). Finally, the use of trifluoroacetic anhydride in catalytic amounts at rt gave rise to the formation of **3a** in good yields (Table 1, entry 6).

These reaction conditions⁹ were extended to the conjugate addition of **2a** with other boronic acids **1** and to the reaction of several representative simple α , β -unsaturated ketones **2** with **1a**. The results are given in Table 2.

These results put forward that trifluoroacetic anhydride also catalyzed the conjugate addition reaction of chalcone **2a** with 2-arylvinylboronic acids substituted by electron-withdrawing groups on the aryl moiety (Table 2, entries 2–4). However, extensive protodeborylation of the starting material was observed in the presence of an electron-donating group as aryl substituent of **1** (Table 2, entry 5). The reaction did not take place at rt when a 2-alkylvinylboronic acid was used. However, a good yield of the corresponding conjugate addition product was observed when the temperature was increased to 60 °C (Table 2, entries 6 and

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	R ¹ —B(OH) ₂ 1	$\frac{R^3}{(CF_3CO)}$	$\stackrel{O}{\longrightarrow} R^2 \qquad R^1$	0 3	1a , $R^1 = PhCH=CH$ 1b , $R^1 = p - CF_3 - C_6H_4CH=CH$ 1c , $R^1 = p - F - C_6H_4CH=CH$ 1d , $R^1 = p - CI - C_6H_4CH=CH$ 1e , $R^1 = p - MeO - C_6H_4CH=CH$ 1f , $R^1 = p - MeO - C_6H_4CH=CH$ 1f , $R^1 = Ph$	2a, R ² = R ³ = F 2b, R ² = Me, R 2c, R ² = Ph, R ³ 2d, R ² = Et, R ³ 2e, R ² = Me, R 2f, R ² = Ph, R	Ph $R^{3} = Ph$ $R^{3} = Me$ $R^{3} = H$ $R^{3} = Et$ $R^{3} = PhCH=Cl$	2g, 2i, 0 2j, ^{BzO}	$\begin{array}{c} \begin{array}{c} & 2h, \\ & \\ \end{array} \end{array} \begin{array}{c} & Ph \\ OBz \\ & \\ \end{array} \begin{array}{c} & \\ \end{array} \end{array} \begin{array}{c} & Ph \\ \\ \end{array} \begin{array}{c} & \\ \end{array} \end{array}$	
Entry	1	2	T (°C)	3 ^b (%))	Entry	1	2	T (°C)	3 ^b (%)
1 ^c	1a	2a	25	Ph	Ph O Ph 3a (95)	10	1a	2c	25	Ph O Ph 3i (0)
2	1b	2a	25	pCF ₃ -	$-C_6H_4$ Ph O Bb (90)	11	1a	2c	60	Ph O Ph 3i (75)
3	1c	2a	25	pF-C ₆	h_{4} h_{4} h_{4} h_{7} h_{7	12	1a	2d	60	Ph 3j (60)
4	1d	2a	25	pCI-C	H_{4} H_{4} H_{6} H_{4} H_{1} H_{1	13	1a	2e	60	Ph 3k (85)
5	1e	2a	25	<i>p</i> MeC	Ph O	14	1a	2f	60	Ph O Ph 3 l (80)
6	1f	2a	25	ⁿ C ₆ H ₁	Ph O 13 3f (0)	15	1a	2g	60	Ph 3m (65)
7	1f	2a	60	ⁿ C ₆ H ₁	Ph O 13 Ph 3f (75)	16	1a	2h	60	Ph 3n (70) trans : cis = 75 : 25

Table 2 (continued)

Entry	1	2	T (°C)	3 ^b (%)	Entry	1	2	T (°C)	3 ^b (%)
8 ^d	1g	2a	60	Ph O Ph J Ph J Ph 3g (75)	17	1a	2i	25	OH HO Ph 30 (80) syn : anti = 50 : 50
9	1a	2b	25	$Ph \xrightarrow{0} Ph \xrightarrow{0} Ph$	18	1a	2j	25	$BzO \xrightarrow{OBz} Ph$ $BzO \xrightarrow{Ph} O$ $BzO \xrightarrow{Ph} O$ $Syn: anti = 20:80$

 a 1 (1.25 equiv), 2 (1.0 equiv), (CF_3CO)_2O (0.3 equiv), CH_2Cl_2 (1.6 mL/mmol), 18 h. b Isolated yield.

^c See Table 1 (entry 6).
 ^d Reaction carried out with 1.0 equiv of (CF₃CO)₂O.

Table 3

Conjugate addition of **2** with **1** in the presence of AcCl^a



No.	1	2	T (°C)	3 ^b (%)	4 ^b (%)
1 ^c	1a	2a	25	Ph O Ph 3a (90)	_
2	1b	2a	25	$pCF_{3}-C_{6}H_{4}$ Ph O 3b (80)	-
3	1e	2a	25	pMeO-C ₆ H ₄ Ph O 3e (10)	_
4	1f	2a	60	$n_{C_6H_{13}} \xrightarrow{Ph O}_{Ph}$ 3f (75)	CI O Ph 4a (10)
5	1a	2b	25	Ph O Ph O 3h (50)	_
6	1a	2c	25	Ph 3i (30)	Cl O Ph 4b (25)
7	1a	2d	25	Ph 3j (20)	CI 4c (65)
8	1a	2f	60	Ph O Ph 3l (70) Ph	_

 a **1** (1.25 equiv), **2** (1.0 equiv), AcCl (1.6 mL/mmol), 18 h. b lsolated yield.

^c See Table 1 (entry 5).

7). On the other hand, no reaction of **2a** with phenylboronic acid **1f** was observed even at 60 °C when a catalytic amount of trifluoroacetic anhydride was used as the promoter. However, it was possible to promote the addition of **1f** using a stoichiometric amount of the promoter at 60 °C (Table 1, entry 8).

Whereas arylketone **2b** reacted with **1a** at rt in the presence of catalytic amounts of trifluoroacetic anhydride similarly to chalcone **2a** (Table 2, entry 9), no reaction was observed with the 4-aryl- α , β -unsaturated alkylketone **2c** (Table 2, entry 10). However, the reaction took place at 60 °C (Table 2, entry 11). Thus, the comparison between **2a**, **2b**, and **2c** in their reactions with **1a** (Table 2, entries 1 and 9–11) showed that arylketones are better substrates than alkylketones in this type of transformation. Consequently, the reactions between **1a** and ketones **2d**, **2e** took place only at 60 °C (Table 2, entries 12 and 13). The addition to dienylketone **2f** occurred exclusively in 1,4-fashion in moderate yield (Table 2, entry 14).¹⁰

Compounds **2g** and **2h** represent interesting substrates, as the conjugate addition of alkenylboronic acids to β,β-disubstituted carbonyl compounds has no literature precedents.¹¹ The addition of 1a to 2g took place with good yield under trifluoroacetic anhydride catalysis at 60 °C (Table 2, entry 15). In a similar fashion, the reaction with pulegone (2h) proceeded in good yield to afford a 70:30 diastereomeric mixture of the conjugate addition products 3h (Table 2, entry 16). Finally, we have considered the stereoselective conjugate addition to the optically pure linear γ , δ -oxygen-functionalized α,β -unsaturated ketones **2i** and **2j** (Table 2, entries 17 and 18). We observed that although the reaction with the isopropylidene derivative 2i afforded the corresponding deprotected conjugate addition products **30** unselectively,^{12,13} the diastereoselectivity of the process could be improved by replacement of the OH-protective groups by benzoyl in favor of the anti addition product.

Despite we have centered most of our synthetic efforts in the catalytic use of trifluoroacetic anhydride at rt, our initial results using AcCl as the solvent deserve some further comments, as these reaction conditions can be attractive for large-scale preparations due to the simplicity of the experimental procedure.¹⁴ We observed that chalcone **2a** also reacted with the electron-deficient 2-arylalkenylboronic acid 1b under these reaction conditions, while extensive decomposition was noticed with the electron-rich 1e (Table 3, entries 1-3). The reaction was also possible with the 2alkylalkenylboronic acid **1f** at 60 °C, but the conjugate addition product was contaminated with small amounts of 4a, formed by HCl addition to 2a (Table 3, entry 4). The reactions of 1a with ketones **2b-d** took place with low yield, and in the case of **2c** and 2d also contaminated with the corresponding HCl addition products **4b**,**c** (Table 3, entries 5–7). On the other hand, a good yield of the 1,4-addition product 31 was observed in the reaction of 1a with dienylketone 2f (entry 8). Thus, the usefulness of the AcClpromoted conjugate addition seems limited to chalcone derivatives and 2-arylvinylboronic acids.

In conclusion, the reaction of vinylboronic acids with α , β -unsaturated ketones catalyzed by trifluoroacetic anhydride constitutes a useful method for conjugate addition under metal-free and experimentally simple conditions.

Acknowledgments

S.R. thanks the government of Spain and for FPU Grant No. AP20090051. Project CTQ2010-16170 from the Spanish government (MICINN) and GR35/10-A from UCM are gratefully acknowledged for financial support. Professor J. Plumet is thanked for useful comments and suggestions.

Supplementary data

Supplementary data (copies of ¹H and ¹³C NMR spectra of compounds **3** and **4**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.105.

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