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Organocatalyzed synthesis of optically active cyanohydrins starting from alpha-ketoesters†

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Abstract: The synthesis of highly functionalized optically active cyanohydrins is described by performing the organocatalyzed selective addition of trimethylsilyl cyanide to a set of alpha-ketoesters employing different (thio)ureas as hydrogen bond catalysts. By optimizing certain parameters that affect to the organocatalytic process, as the temperature, solvent or cyanide concentration, it is possible to obtain the corresponding chiral cyanohydrins with excellent conversions and moderate to good optical purities.

Keywords: Organocatalysis; Thioureas; Chiral cyanohydrins; Process optimization

1. Introduction

Optically active cyanohydrins are very valuable compounds in organic chemistry, as these functionalized molecules can serve as synthons for a wide set of high value compounds, as α-hydroxyketones, α-hydroxyacids, α-halonitriles or β-aminoalcohols, among others [1]. Different approaches have been developed for the preparation of chiral cyanohydrins, but the selective addition of a cyanide source to a carbonyl compound is the most common procedure. Several types of catalysts have been described for this selective process, including metal catalysts, biocatalysts or organocatalysts [2,3].

The use of relatively small organic molecules is an area in constant development since the beginning of this century [4-6], and the use of hydrogen bond catalysts, in which the activation is performed by establishing a set of hydrogen bonds between the catalyst and the starting material, is a well-established technique in chemical synthesis [7,8]. Thus, different ureas and thioureas have been employed for the synthesis of chiral cyanohydrins, achieving in general the best results in presence of Jacobsen type (thio)ureas [9], or cinchona based catalysts [10]. Both types of hydrogen bond catalysts are bifunctional compounds, presenting in their structure a tertiary amine group, which is able to activate the cyanide nucleophile in addition to the electrophile activation debt to the (thio)urea moiety hydrogen bond formation [11]. The use of silyl cyanides as cyanation reagents has gained a great interest in the last few years, as these compounds present a good reactivity and they do not show the volatility and toxicity issues debt to hydrogen cyanide.

In the present proceeding, we are going to describe the use of different (thio)ureas for the preparation of chiral cyanohydrins derived from α-ketoesters, with the aim of obtaining a set of highly functionalized chiral compounds.

2. Methods

*2.1. General procedure for the organocatalyzed cyanosilylation of ketoesters **1-5a** in the optimized conditions*

The corresponding α-ketoester **1-5a** (0.6 mmoles) was dissolved in toluene (1.0 mL) containing *p*-nitrophenol (0.06 mmoles), catalyst **VIb** (0.06 mmoles, compound **5a**) or catalyst **VIIIb** (0.06 mmoles, compounds **1-4a**) and the system was cooled down to -45ºC. After 10 minutes, trimethylsilylcyanide (1.5 equivalents) was added dropwise and the reactions were stirred at -45ºC for the times established. After this, a saturated solution of ammonium chloride (2.0 mL) was added to the crude reaction and the reaction was extracted with ethyl acetate (2 x 5.0 mL). The organic phases were washed with brine (5.0 mL), dried onto sodium sulphate and the solvent was evaporated. The reactions were purified by column chromatography (toluene/EtOAc mixtures) to yield the corresponding *O*-silylated cyanohydrins (–)-**1-5b** with yields of 88% for (–)-**1b**, 92% for (–)-**2b**, 94% for (–)-**3b**, 90% for (–)-4**b** and 76% for (–)-**5b**.

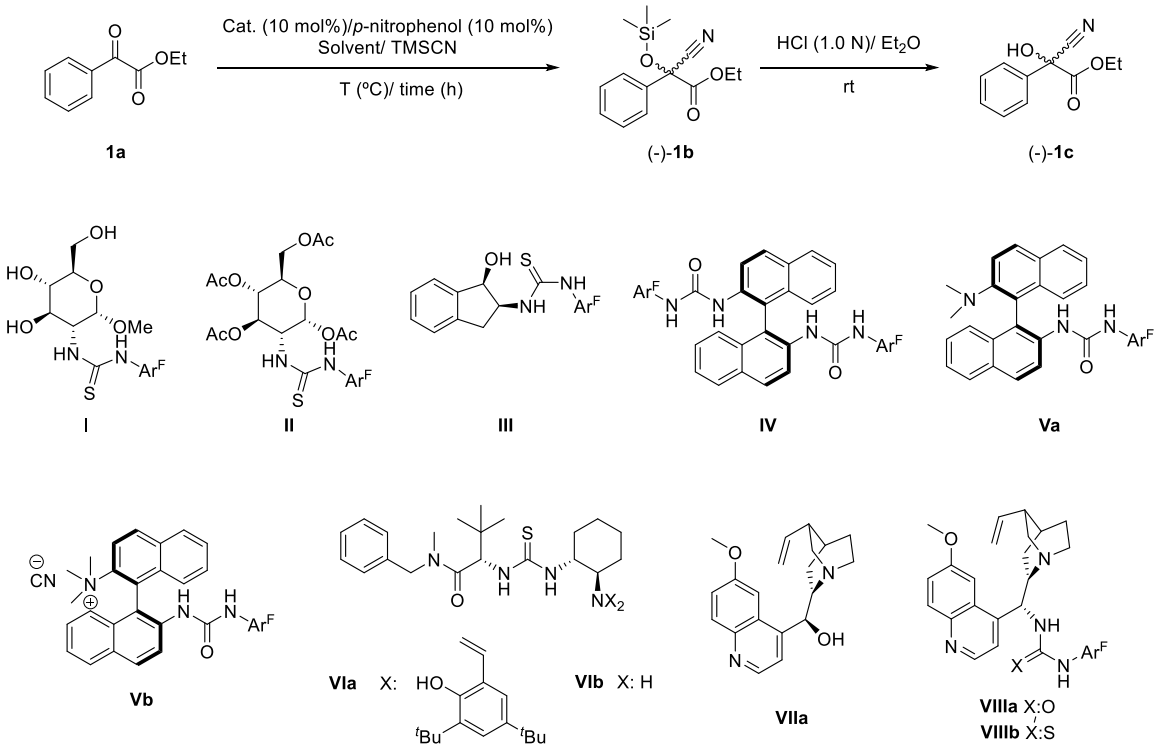
*2.2. General method for the hydrolysis of O-silylated cyanohydrins (–)-**1-5b**.*

The corresponding *O*-silylated cyanohydrin (–)-**1-5b** was dissolved in diethyl ether (1.0 mL) and at room temperature an aqueous solution of HCl 1.0 N (1.0 mL) was added. After 2-3 hours it was observed the complete disappearance of the starting material (TLC in *n*-hexane/EtOAc mixtures). Once finished, the reaction was extracted with EtOAc (2 x 5 mL), dried onto sodium sulphate and the solvent was evaporated under reduced pressure to yield the free cyanohydrins (-)-**1-5c** without further purification (yields higher than 90%).

3. Results and discussion

Our initial studies were performed in the cyanosilylation of ethyl benzoylformate **1a** in toluene employing 1.5 equivalents of trimethylsilyl cyanide (TMSCN) as mild cyanide source in presence of different (thio)ureas as organocatalysts (Scheme 1). The obtained *O*-silylcyanohydrins can be easily transformed into the free cyanohydrins by mild treatment with a diluted aqueous solution of HCl (1.0 N) and THF, obtaining in all cases quantitative yields. Initially, we have tested the sugar-based thioureas **I-II**, which have been prepared in our research group and employed in the selective addition of formaldehyde *tert*-butylhydrazone to aliphatic α-ketoesters (entries 1 and 2, Table 1) [12]. After long times, low conversions were obtained while the final product was obtained almost racemic. The use of an indanol-based thiourea as **III** also led to a poor cyanosilylation reaction. Only 8% of (–)-**1b** was recovered after 70 hours at -15ºC.

The BINAM-derived bis-urea **IV**, that has been also successfully employed in the formaldehyde *tert*-butylhydrazone addition to aromatic α-ketoesters [13], did not catalyze the cyanosilylation at -30ºC even after 72 hours. By this reason, we have prepared a BINAM-monourea containing a tertiary amine in its structure (catalyst **Va**) [14]. The cyanosilylation catalyzed by this compound afforded the *O*-silylated cyanohydrin with 78% conversion after 40 hours, and a modest selectivity (entry 5). Further *N*-methylation of **Va** and treatment with a cyanide salt afforded the quaternary ammonium-thiourea **Vb**. The use of this catalyst allows a slight increase in both the activity and selectivity, as shown in entry 6, being possible to achieve (–)-**1b** with 86% conversion and 25% *ee*.



Scheme 1. Cyanosilylation of ethyl benzoylformate **1a** catalyzed by a set of (thio)ureas. Ar^F refers to the bis-3,5-trifluoromethylphenyl group.

Table 1. Organocatalyzed cyanosilylation of prochiral ethyl benzoylformate (**1a**) in toluene.[1]

Entry	Catalyst	T (ºC)	time (h)	Conversion (%)[2]	*ee* (%)[3]
1	**I**	-15	72	13	≤3
2	**II**	-15	48	27	8
3	**III**	-15	70	8	n.d.
4	**IV**	-30	72	≤3	n.d.
5	**Va**	-45	40	78	17
6	**Vb**	-45	24	86	25
7	**VIa**	-45	24	80	41
8	**VIb**	-45	40	83	27
9	**VII**	-45	24	92	5
10	**VIIIa**	-45	24	≥97	48
11	**VIIIb**	-45	24	86	63

[1] For reaction details, see Experimental Section. [2] Determined by ^{1}H-NMR in $CDCl_3$. [3] Determined by HPLC after hydrolysis to the free cyanohydrin (–)-**1c**. n.d. not determined.

In view of these results, we decided to test two Jacobsen type thioureas (**VIa-b**), which have been previously employed in cyanosilylation processes. As shown in entry 7, the thiourea presenting an imine moiety in its structure allowed to obtain (–)-**1b** with 41% *ee* and a conversion of 80% after 24 hours. When the thiourea contains a primary amine (**VIb**, entry 8), the optical purity of the cyanohydrin decayed to 25% while the reaction was slower (83% conversion after 40 h). Quinine was able to perform the cyanosilylation of α–ketoester **1a** with a 92% conversion after 24 hours, but without selectivity (entry 9). Thus, we have prepared both a cinchona-based urea (**VIIIa**) and thiourea (**VIIIb**) containing a 3,5-bistrifluoromethylphenyl group in order to increase the system reactivity [15]. Both catalysts were able to catalyze the cyanosilylation of **1a** with good performance in toluene at -45ºC. Thus, the use of urea **VIIIa** afforded (–)-**1b** with complete conversion and 48% *ee* after 24 hours, while the reaction in presence of the thiourea **VIIIb** was slower (86% conversion in

the same time) but showed the highest enantioselectivity (63% *ee*). Once selected the cinchona-based (thio)ureas **VIIIa-b** as the most suitable organocatalysts for the cyanosilylation of substrate **1a**, we have studied some of the reaction parameters than can affect to the process activity and selectivity. Initially, the reaction catalyzed by urea **VIIIa** at -45ºC has been tested in different organic solvents, as shown in Table 2. Conversions higher than 90% can be achieved using *tert*-butyl methyl ether (entry 2) or dichloromethane (entry 3), while the use of diethyl ether and hexane afforded lower activities. For all the solvents tested, much lower selectivities were obtained compared to toluene.

Table 2. Solvent effect in the synthesis of cyanohydrin (–)-**1b** catalyzed by urea **VIIIa** at -45ºC after 24 hours.

Entry	Solvent	Conversion (%)[1]	*ee* (%)[2]
1	Toluene	≥97	48
2	*tert*-Butyl methyl ether	90	29
3	Dichloromethane	96	26
4	Diethyl ether	83	36
5	*n*-Hexane	78	33

[1] Determined by ^{1}H-NMR in $CDCl_3$. [2] Determined by HPLC after hydrolysis to the free cyanohydrin (–)-**1c**.

The effect of the temperature in the organocatalyzed addition of TMSCN has been also studied in the **VIIIa**-organocatalyzed addition, as shown in Figure 1. As the reactions were stopped at different times for each temperature, we have defined the reaction rate as the mmoles of substrate **1a** consumed per hour and per mL, in order to compare the conversions obtained. As expected, the increase of the temperature led to an important increase in the reaction rate, from 0.7 mmol mL^{-1} h^{-1} at -78ºC up to 4.9 mmol mL^{-1} h^{-1} at -15ºC, but also to a high decrease in the system selectivity, especially at temperatures higher than -45ºC, as the optical purity of (–)-**1b** passed from 48% at -45ºC to 21% at -30ºC.

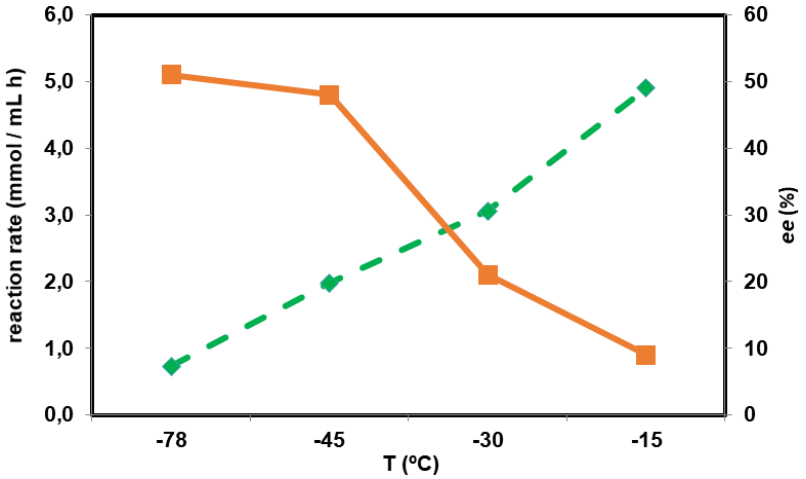


Figure 1. Effect of the temperature in the activity (dashed green line) and the selectivity (continuous red line) of the cyanosilylation of ethyl benzoylformate **1a** catalyzed by thiourea **VIIIb** in toluene.

Once selected this temperature as the best for the process, we have analyzed the influence of the cyanide source concentration in the reaction, as shown in Table 3. The use of higher amounts of cyanide afforded slightly higher reaction rates but also led to an important decrease in the system selectivity. Thus, when the cyanosilylation was performed with 5.0 equivalents of cyanide (entry 4) (–)-**1b** was recovered with only 13% *ee*. The use of 1.0 equivalent of cyanide does not increase the optical purity of the final product, but the reaction rate suffers an important decrease, as shown in entry 1. It can be established that 1.5 equivalents results to be a proper amount for this process.

Table 3. Effect of the trimethylsilyl cyanide in the cyanosilylation of **1a** catalyzed by thiourea **VIIIa** at -45ºC after 24 hours.[1]

Entry	Cyanide equivalents	Rate (mmol L^{-1} h^{-1})	*ee* (%)[2]
1	1.0	12.3	47
2	2.0	48.4	48
3	2.0	54.6	43
4	5.0	57.2	13

[2] Determined by ^{1}H-NMR in $CDCl_3$. [3] Determined by HPLC after hydrolysis to the free cyanohydrin (–)-**1c**.

Acetone cyanohydrin has been also employed as cyanide source instead of trimethylsilyl cyanide. The use of this reagent allows obtaining directly the free cyanohydrin without requiring a hydrolysis step. Unfortunately, the reaction of **1a** in toluene catalyzed by thiourea **VIIIb** afforded 85% conversion after 36 hours, while (–)-**1b** was obtained with only 37% *ee*.

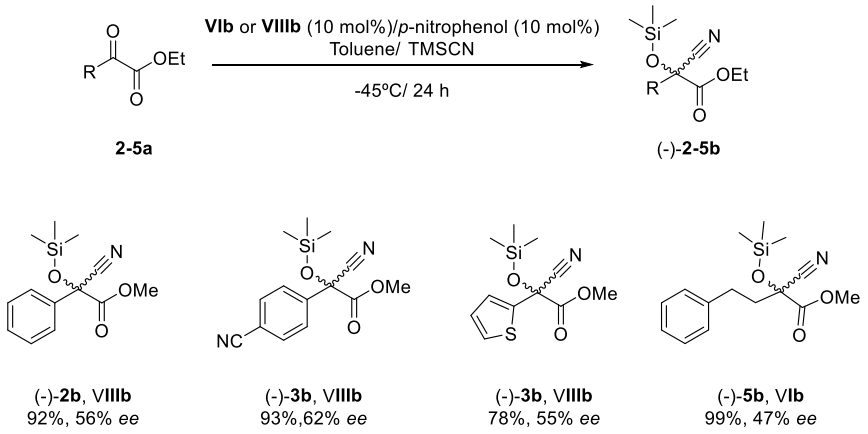
It has been described that the presence of certain additives as alcohols and phenols in organocatalyzed cyanosilylation has a positive effect in both the activity and selectivity of the reactions, as these additives can improve the formation of the cyanide nucleophile in the reaction medium. By this reason, we have studied the use of three alcohols in 10 mol% extent in the **VIIIb**-catalyzed cyanosilylation of ethyl benzoylformate **1a**. As can be observed in Table 4, all the three alcohols increased the systems activity, being possible to recover (–)-**1b** with conversions higher than 90% after 24 hours. Regarding the selectivity, the addition of 10 mol% of *p*-nitrophenol allows to increase the process selectivity, as the chiral cyanohydrin was obtained with 68% *ee*, while for the aliphatic alcohols, the final product is recovered with slightly lower selectivity.

Table 4. Cyanosilylation of ketoester **1a** catalyzed by **VIIIb** in presence of different alcohols as additives at -45ºC after 24 hours.

Entry	Additive	Conversion (%)[1]	*ee* (%)[2]
1	None	86	63
2	2,2,2-trifluoroethanol	93	56
3	*tert*-butanol	92	61
4	*p*-nitrophenol	95	68

[1] Determined by ^{1}H-NMR in $CDCl_3$. [2] Determined by HPLC after hydrolysis to the free cyanohydrin (–)-**1c**.

In order to explore the substrate profile of this organocatalyzed process, the best conditions found for compound **1a** (toluene, -45ºC and 10 mol% thiourea **VIIIb** and 10 mol% of *p*-nitrophenol) were then extended to other aromatic α-ketoesters, as shown in Scheme 2. Thus, methyl benzoylformate reacted with TMSCN leading to (–)-**2b** with 92% conversion and 56% *ee*, slightly lower than the achieved for the ethyl analogue. The cyanosilylation of ethyl 4-cyanobenzoylformate **3a** occurred with 93% conversion after 24 hours, recovering (–)-**3b** with 62% *ee*. A heteroaromatic α-ketoester as **4a** was also converted in the (–)-*O*-silylcyanohydrin, but with a lower conversion and optical purity (55% *ee)* than its aromatic analogue **1a**.



Scheme 2. Substrate scope in the organocatalyzed cyanosilylation of α-ketoesters employing thioureas **VIb** and **VIIIb**.

The cyanosilylation of ethyl 4-phenyloxobutyrate (**5a**) in presence of the cinchona-based thiourea **VIIIb** afforded the *O*-silyl cyanohydrin with a good activity but with a low selectivity (33% *ee*). This α-ketoester is not an aromatic one, as the reactive center is linked to an aliphatic carbon atom, which can explain its different behavior. We have tested other catalysts in its cyanosilylation, achieving the best results in presence of the Jacobsen thiourea **VIb**. In these conditions, (–)-**5b** was recovered with complete conversion and a 49% *ee* after 24 hours.

4. Conclusions

The cyanosilylation of a set of prochiral α-ketoesters catalyzed by different (thio)ureas allows obtaining the corresponding chiral *O*-silyl cyanohydrins presenting an ester moiety with high conversions and moderate optical purities. Different parameters that can affect to the organocatalyzed process have been optimized (temperature, cyanide source and its concentration, solvent, additives), in order to achieved the highest optical purities. Thus, best conditions for the cyanosilylation of aromatic substrates were achieved with a cinchona-based thiourea in toluene at -45ºC in presence of 10 mol% of *p*-nitrophenol, while for the aliphatic substrate the highest selectivity was obtained with a Jacobsen type thiourea. This process represents the first step to obtain chiral functionalized cyanohydrins, valuable synthons in organic synthesis.

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Author Contributions: G.d.G performed the experiments, conceived, designed and wrote the paper.

Conflicts of Interest: The author declares no conflict of interest.

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