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Conjugated addition of bis(oxazolinyl)zinc to substituted 2-nitrovinyl benzenes: an alternative synthesis of (±)-Rolipram

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Abstract—In this letter we present a new 2,4,4-trimethyl-2-oxazoline anion-zinc derivative that has a remarkable thermal stability when compared with the corresponding cyanocuprate counterpart. The yields from conjugated addition to several 2-nitrovinyl benzenes are moderate to good and the reaction itself is easier to execute and cleaner. As an application, this methodology was applied to an alternative synthesis of (±)-Rolipram, a drug with several interesting biological activities.

1. Introduction

Conjugated addition is a recognized method for the construction of new carbon–carbon bond employing an organometallic compound.[1] Conversely, nitroolefins are powerful Michael acceptors and versatile intermediates, since the nitro group can be converted into a variety of functional groups, among them, an amino group.[2] Organozinc compounds generally display a remarkable functional group tolerance[3] and polyfunctional molecules can be obtained by the conjugate addition of this type of reagent. However, the results are dependent not only on the structure of the Michael acceptor but also on the nature of the nucleophile to be transferred.[4,5]

As pointed out previously,[6] the 1,4-transfer of the 2,4,4-trimethyl-2-oxazoline anion (**1**) would be very useful as a carboxymethyl equivalent addition procedure. As expected, the addition of lithiated anion (**1**) to α,β-unsaturated systems yielded ~20% of the 1,4-addition product in a complex mixture of side products. In fact, the conjugated addition of bis(oxazolinyl)cyanocuprates (**2**) to α,β-unsaturated systems has been recently reported and was applied to the synthesis of lactams, and δ or γ-amino acids.[7,8] However, the thermal stability of cyanocuprates (**2**) was a major drawback and compound (**2**) readily decomposes above −30 °C limiting its applications. To overcome this limitation, we decided to investigate the thermal stability and chemical reactivity of the zinc derivative[9] (**3**), as shown in Figure 1.

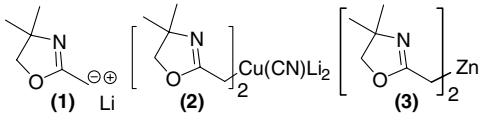
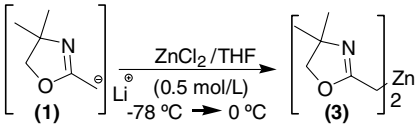


Figure 1. 2,4,4-Trimethyl-2-oxazoline anion derivatives.

2. Results and discussion

Compound (**3**) was available from the reaction of 2,4,4-trimethyl-2-oxazoline anion (**1**) and a stock solution of $ZnCl_2$ (0.5 mol/L) in THF at −78 °C (Scheme 1). The resulting bis(oxazolinyl)zinc (**3**) shows remarkable thermal stability and is easier to obtain than compound (**2**).

In order to understand the scope and limitations of this system, bis(oxazolinyl)zinc (**3**) was reacted with the 2-nitrovinyl benzene derivatives (**4**–**8**), which were prepared by condensing nitromethane with an appropriate aromatic aldehyde.[10] The results are summarized in Table 1.



Scheme 1.

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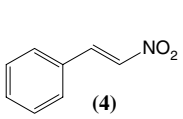
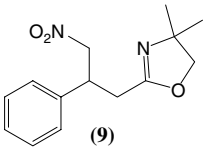
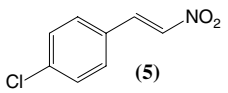
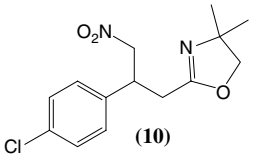
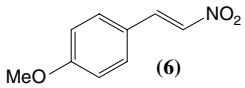
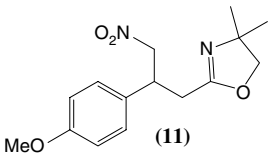
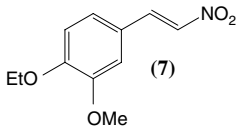
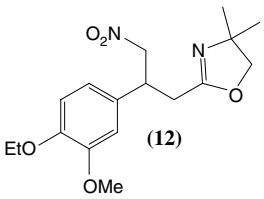
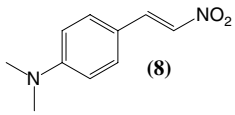
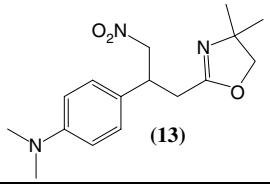
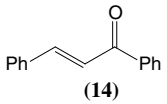
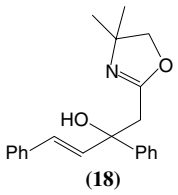
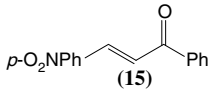
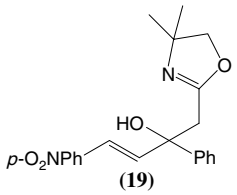
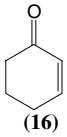
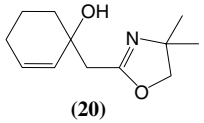
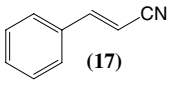
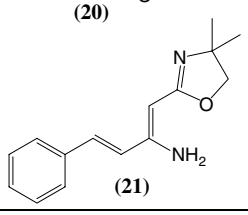
Table 1.

Electrophile[b]	Product	(%)[a]
 (4)	 (9)	95
 (5)	 (10)	73
 (6)	 (11)	70
 (7)	 (12)	60
 (8)	 (13)	15

[a] Isolated yield.
[b] All compounds were identified by ^{1}H NMR and ^{13}C NMR and gave consistent data.

Table 2.

Electrophile[b]	Product	(%)[a]
 (14)	 (18)	95
 (15)	 (19)	93
 (16)	 (20)	80
 (17)	 (21)	80

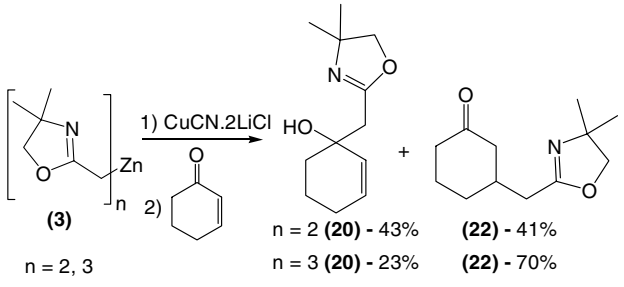
[a] Isolated yield.
[b] All compounds were identified by ^{1}H NMR and ^{13}C NMR and gave consistent data.

The addition of bis(oxazolinyl)zinc (**3**), to 2-nitrovinyl benzene (**4**) at −78 °C, followed by slow warming to room temperature, yielded (**9**) in a 95% yield.[11] This reaction gave consistent results, even after maintaining compound (**3**) for 5 h at 0 °C before the addition of (**4**). No *ypso*-type substitution product was detected.[12] All the yields obtained are moderate to good and the reactions were clean and easy to purify. An exception was the amino compound (**8**), which gave a poor addition result, probably due to its low solubility in cold THF.[13]

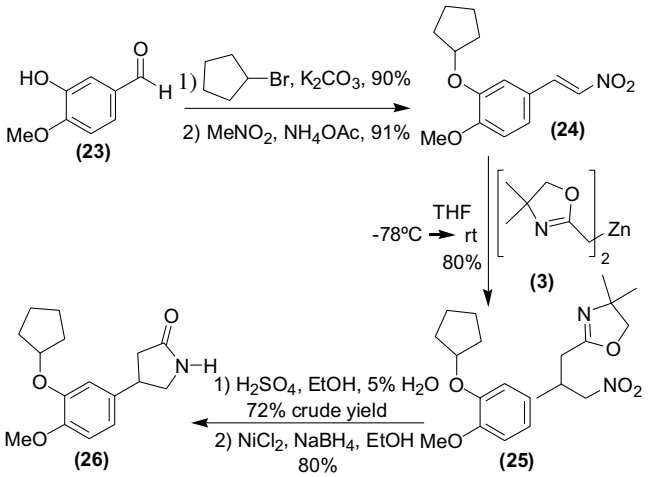
Besides 2-nitrovinyl benzene derivatives, three enones (**14**–**16**) and one 2-cyanovynil benzene derivative (**17**) were also tested as electrophiles. As expected, only 1,2-addition compounds were isolated in excellent yields (Table 2). However, the addition of compound (**3**) to the cyanoalkene derivative (**17**) gave a result similar to the one reported by Fustero et al.[14] using saturated nitriles (Blaise reaction).[15] In our example, compound (**21**) was isolated as a mixture of isomers.

Another attempt to modify the chemical reactivity of (**1**) was made by using copper cyanide salt[16] as the additive and changing the lithium anion/zinc ratio. The addition of CuCN·2LiCl to compound (**3**), at −78 °C followed by a slow warming to 0 °C, presumably generates the corresponding zinc cyanocuprate, which was immediately reacted with 2-cyclohexen-1-one, yielding a mixture of 1,2 and 1,4 addition products as shown in Scheme 2. Adding a third equivalent of oxazoline lithium anion to the zinc cyanocuprate above gave better 1,4 addition results and exhibits a similar thermal stability.

This methodology was successfully applied to the synthesis of (±)-Rolipram[17] (**26**) (a γ-lactam), which is an inhibitor of (PDE)-IV,[18] a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase. Rolipram also is employed in the treatment of depression.[19] To accomplish this synthesis, 2-nitrovinyl benzene substrate (**24**)[20] was prepared in two steps from isovanilin (**23**) in an 82% overall yield. The addition of bis(oxazolinyl)zinc (**3**) to (**24**) afforded, after work up, compound (**25**)[21] in an 80% yield. Compound (**25**) was then hydrolyzed and esterified[22] to the corresponding ethyl ester in a 72% crude yield. The resulting mixture was reduced[23]



Scheme 2.



Scheme 3.

to the corresponding amino ester to form lactam (**26**)[24] in an 80% yield (Scheme 3).

Acknowledgements

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11. *General procedure*: A flask containing 2,4,4-trimethyl-2-oxazoline (0.535 mL, 4.2 mmol) and 9 mL of THF under argon, was cooled in a dry ice/acetone bath (−78 °C) and *n*-BuLi (4.2 mmol) was added dropwise. After stirring for 30 min at −78 °C, a solution of $ZnCl_2$ (4.2 mL of 0.5 mol/L in THF) was added to the oxazoline anion and the resulting solution was stirred at −78 °C for 15 min and transferred to an ice bath at 0 °C for 30 min. After this period, the solution was cooled at −78 °C and a solution of appropriate 2-nitrovinyl benzene (2 mmol) in dry THF (4 mL) was added. The reaction was slowly warmed to room temperature, then quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate (3 × 20 mL) and dried over anhydrous Na_2SO_4. The product was isolated by filtration, followed by solvent removal under vacuum and then purified by flash chromatography (ethyl acetate/hexane 2:1). Spectral data of (**9**): ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.10 (s, 3H); 1.18 (s, 3H); 2.67 (d, $J = 7.8$ Hz, 2H); 3.79–3.97 (m, 3H); 4.79 (dd, $J_1 = 12.72$ Hz, $J_2 = 8.02$ Hz, 1H); 4.73 (dd, $J_1 = 12.72$ Hz, $J_2 = 7.05$ Hz, 1H); 7.20–7.33 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 28.18; 32.13; 41.10; 67.18; 79.11; 79.46; 127.40; 127.93; 129.00; 138.38; 162.40.
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21. Spectral data of (**25**): ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.07 (s, 3H); 1.13 (s, 3H); 1.40–1.60 (m, 2H); 1.40–1.90 (m, 6H); 2.59 (d, $J = 7.81$ Hz, 2H); 3.70–3.90 (m, 6H); 4.53 (dd, $J_1 = 12.45$ Hz, $J_2 = 8.05$ Hz, 1H); 4.66 (m, 3H); 6.60–6.80 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 149.88; 147.98; 130.85; 125.63; 119.52; 114.70; 112.37; 80.73; 79.98; 56.22; 40.89; 32.96; 32.34; 28.44; 28.36; 24.21.
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24. Spectral data of (**26**): ^{1}H NMR (200 MHz, $CDCl_3$): 1.50–2.00 ppm (m, 8H); 2.48 (dd, $J_2 = 8.8$ Hz, $J_2 = 17.22$ Hz, 1H); 2.73 (dd, $J_1 = 8.8$ Hz, $J_2 = 16.82$ Hz, 1H); 3.39 (dd, $J_1 = 7.05$ Hz, $J_1 = 8.8$ Hz); 3.50–3.85 (m, 2H); 3.84 (s, 3H); 4.70–4.83 (m, 1H); 6.43 (s, 1H); 6.75–6.87 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): 24.22; 33.02; 38.31; 40.19; 49.98; 56.35; 80.81; 112.43; 114.06; 119.02; 134.74; 148.13; 177.97.