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$P(RNCH_2CH_2)_3N$-catalyzed diastereoselective synthesis of oxazolines

Philip Kisanga,[a,b] Palanichamy Ilankumaran[a,c] and John G. Verkade[a,*]

[a]*Department of Chemistry, Iowa State University, Ames, IA 50011, USA*
[b]*Aldrich Chemical Company, 940 W. St. Paul Ave., Dept. 271, Milwaukee, WI 53233, USA*
[c]*122B, Cedar Lane, Highland Park, NJ 08904, USA*

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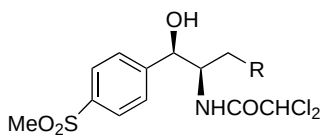
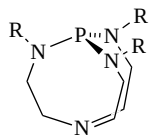
Abstract—We report herein that the strong nonionic bases $P(RNCH_2CH_2)_3N$(R = Me, **1a**; *i*-Pr, **1b**) catalyze the diastereoselective synthesis of thirteen oxazolines in the presence of 5–30% of these catalysts. The formation of the oxazolines proceeds under very mild conditions in good to excellent yields with high diastereoselectivity (>95:5) for the *trans* isomer. © 2001 Elsevier Science Ltd. All rights reserved.

Oxazolines are versatile intermediates in the synthesis of β-substituted serines[1] which are of significant importance because of their utility in the synthesis of various antibiotics.[2] Thus, the serine moiety constitutes the primary core structure of antibiotics, such as hypeptin[2b] and leucinostatin.[3] Ethyl isocyanoacetate, a synthon for the formation of oxazolines, is relatively acidic and can be deprotonated by a variety of bases for coupling with aldehydes to afford oxazolines. However, the lack of diastereoselectivity of such reactions has rendered this synthetic route of limited use. Among catalysts that have been reported to effect the conversion of aldehyde/ether isocyanoacetate mixtures to oxazolines are $ZnCl_2$,[4] a $ZnCl_2$/CuCl system,[5] NaCN/EtOH,[6] and Cu_2O.[7] The copper(I) oxide-catalyzed process leads to the formation of varying ratios (1.5:1.0–0.4:1.0) of diastereomers[7] and this catalyst also induces migration of the imine double bond with the resultant formation of two tautomers, giving a complex mixture of products.[7] Furthermore, the presence of α,β-unsaturation leads to Michael addition, rendering this method of marginally practical utility. Although the NaCN/EtOH system affords oxazoline in high yields,[6] its inability to induce excellent diastereoselectivity with aldehydes other than phenyl acetaldehyde restricts its use.[8] The $ZnCl_2$/CuCl catalyzed process also leads to the formation of diastereomeric mixtures (7:1–1:1, *trans*:*cis*).[5] As a result of these poor selectivities, alternative routes to the β-hydroxy α-amino acids have been developed,[9] among which are the condensation of glycine with aldehydes on Ni(II) complexes[9a] and an electrophilic amination reaction.[9b] Since nickel is highly toxic, this methodology is not attractive in an industrial setting. The electrophilic amination process required 2.5–4.2 equiv. of LDA and also 1.5 equiv. of di-*t*-butylazodicarboxylate.[9b] Moreover, the diastereoselectivity in this reaction ranges from 94:6–75:25 (*trans*:*cis*).[9b] The use of excess LDA as a base has been reported to effect the reaction of ethyl isocyanoacetate with *o*-anisaldehyde to give the corresponding oxazoline in 80% yield at −75°C.[9c] Enzyme systems[10] have also been investigated for the synthesis of the broad spectrum antibiotic thiamphenicol **1a** and florfenicol **2a**.[10c]



1a R = OH
1b R = F



2a R = Me
2b R - *i*-Pr

The proazaphosphatranes **2a** and **2b**[11] first synthesized in our laboratories have recently attracted interest as versatile highly basic[12] catalysts and reagents for variety of useful transformations.[13–24] We therefore decided to explore additional examples of reactions in which stereoselectivity is an issue. Since oxazolines are versatile intermediates for the synthesis of serine derivatives, which in turn could open a route to interesting unnatural amino acids, we decided to investigate the

Keywords: oxazolines; proazaphosphatranes; catalysts; diastereoselectivity; nonionic base.

* Corresponding author. Tel.: (515) 294-5023; fax: (515) 294-0105; e-mail: jverkade@iastate.edu

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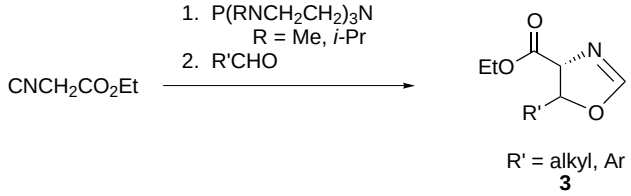

Scheme 1.

possibility of inducing a diastereoselective reaction between aldehydes and ethyl isocyanoacetate (Scheme 1).

We report here the use of catalytic amounts of the proazaphosphatranes **2** as catalysts in the synthesis of oxazoline alkyl carboxylates with high diastereoselectivity. The reaction of benzaldehyde with ethyl isocyanoacetate in THF in the presence of 20% of **2b** at room temperature for 1 h afforded a product mixture that contained the *trans*-oxazoline **3a** as the major product according to the ^{1}H NMR spectroscopy. However, the reaction was not clean and led to the formation of other uncharacterized side products. No significant improvement was observed upon reducing the temperature to −78°C or raising the temperature to 40°C. However, upon changing the solvent to isobutyronitrile, the desired oxazoline ethyl carboxylate **3a** was isolated in 95% yield.[25] Both **2a** and **2b** afforded similar yields within experimental error (data for **2a** not shown in Table 1).

Table 1. Reaction of aldehydes with ethyl isocyanoacetate in isobutyronitrile to give **3**

Aldehyde	Mol% **2b**	*T*, °C (*t*, min)	Yield of **3**, %
Benzaldehyde	0.20	25 (60)	**3a**, 95
p-Fluorobenzaldehyde	0.20	−5 (15)[a]	**3b**, 98
p-Chlorobenzaldehyde	0.20	−20 (15)[a]	**3c**, 94[b]
p-Cyanobenzaldehyde	0.30	−63 (75)	**3d**, 99
p-Nitrobenzaldehyde	0.30	−63 (75)	**3e**, –[d]
p-Anisaldehyde	0.20	25 (120)	**3f**, 78
p-Methylsulfonylbenzaldehyde	0.30	25 (75)	**3**, 97
2,5-Dimethylbenzaldehyde	0.30	−63 (960)	**3h**, 93[b]
2,5-Dimethoxybenzaldehyde	0.30	25 (90)	**3**, 91
Isobutyraldehyde	0.05	25 (60)[c]	**3o**, –[e]
Pivalaldehyde	0.05	−25 (60)[c]	**3k**, 87
n-Heptaldehyde	0.05	−25 (60)[c]	**3l**, –[e]
(*E*)-Cinnamaldehyde	0.20	−25 (75)[c]	**3m**, 68
n-Butyraldehyde	0.05	−25 (60)[c]	**3a**, –[e]
o-Anisaldehyde	0.20	25 (60)	**3o**, 75
2-Naphthaldehyde	0.20	25 (60)	**3p**, 97
2-Furaldehyde	0.20	25 (60)	**3q**, 93

[a] This was followed by stirring at room temperature for 60 min.
[b] Very small amounts (2–3%) of the *cis*-isomer were observed by ^{1}H NMR spectroscopy of the crude reaction mixture.
[c] The reactants were mixed at −63°C, stirred for 15 min and then at rt for time periods specified.
[d] An inseparable mixture containing the Knoevenagel product was observed even at −63°C overnight.
[e] An inseparable complex mixture containing the oxazoline, the Knoevenagel product and unidentified materials was observed by ^{1}H NMR spectroscopy.

Comparison of the ^{1}H and ^{13}C NMR data for product **3a** to literature data[5] revealed that the *trans*-oxazoline ethyl carboxylate was the only product of the reaction. Attempted reaction of *p*-fluorobenzaldehyde in isobutylnitrile afforded complex reaction mixtures. However, by carrying out the reaction with ethyl isocyanoacetate at a lower temperature (see Table 1) for 15 min followed by further reaction at room temperature for 1–1.5 h, *p*-fluorobenzaldehyde, *p*-chlorobenzaldehyde, *p*-methylsulfonylbenzaldehyde and pivalaldehyde reacted to afford the corresponding *trans*-oxazoline ethyl carboxylates, in addition to small amounts of the corresponding Knoevenagel products in the cases of *p*-methylsulfonylbenzaldehyde and pivalaldehyde as shown by ^{1}H NMR spectroscopic analysis. On the other hand aromatic aldehydes bearing electron donating groups (2,5-dimethylbenzaldehyde, 2,5-dimethoxybenzaldehyde, *o*-anisaldehyde, 2-naphthaldehyde and 2-furaldehyde required room temperature to afford similar yields (Table 1) with the exception of 2,5-dimethylbenzaldehyde which consistently formed large amounts of the Knoevenagel product. However, by reducing the temperature to −63°C and carrying out the reaction for 16 h followed by quenching with MeOH at −40°C, clean formation of the desired oxazoline ethyl carboxylate was realized with 2,5-dimethylbenzaldehyde. Nitrobenzaldehyde consistently formed a mixture of the oxazoline and a Knoevenagel product that could not be separated. The oxazoline ethyl carboxylate **3g** thus obtained in 97% yield is of significance because an analogous oxazoline has previously been used as an intermediate in the synthesis of thiamphenicol (**1a**) and florfenicol (**2b**).[10b,c] The aliphatic aldehydes isobutyraldehyde, *n*-heptaldehyde, and *n*-butyraldehyde gave complex mixtures consisting of desired compounds, the Knoevenagel products and other unidentified species.

Acknowledgements

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25. The desired amount of **2b** (Table 1) was weighed into a flask under nitrogen. To this was added 3.0 mL of isobutyronitrile, followed by 2.0 mmol of ethyl isocyanoacetate. The reaction mixture was placed in a constant temperature bath adjusted to the temperature indicated in Table 1 and stirred for 5 min. To this solution was added 2.0 mmol of the aldehyde and then the solution was stirred at this temperature for a further 15 min after which it was allowed to stir at room temperature for 1 h. The reaction mixture was loaded onto a small silica gel column and eluted with ethyl ether. Removal of the solvent in vacuo afforded a crude mixture that was purified by eluting it on a silica gel column with ether/hexane. The ratio of ether was increased in 5% increments. The oxazolines eluted with 40% ether in hexane. The more polar oxazolines **3b–e** and **3g** were purified by eluting them with incrementally increasing amounts (5%) of ethyl acetate in hexane. They eluted 40% ethyl acetate in hexane. Compound **3a**: see discussion; **3b**: ^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3H), 4.30 (q, 2H), 4.575 (dd, 1H), 5.66 (d, 2H), 7.090 (AB q, 2H), 7.31 (AB q, 2H). ^{13}C NMR ($CDCl_3$): δ 170.3, 164.1, 161.6, 156.2, 134.8 (d, $J=3$ Hz), 127.5 (d, $J=8$ Hz), 115.9 (d, $J=22$ Hz), 81.6, 75.5, 62.1, 14.1. HRMS: Calcd for $C_{12}H_{12}FNO_5$ 237.0801, found m/e (M^+) 237.0800; **3c**: Isolated with an inseparable Knoevenagel by-product. ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H), 4.32 (q, 2H), 4.55 (dd, 1H), 5.65 (d, 1H), 7.09 (d, 1H), 7.31–7.25 (m, 2H), 7.39–7.36 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 170.3, 156.2, 137.5, 134.7, 130.8, 129.2, 127.0, 81.5, 75.5, 62.2, 14.2. HRMS: Calcd for $C_{12}H_{12}ClNO_5$ 253.0506, found m/e (M^+) 253.0509; **3d**: ^{1}H NMR ($CDCl_3$): δ 1.35 (m, 3H), 4.32 (dq, 2H), 4.56 (dd, 1H), 5.75 (d, 1H), 7.14 (d, 1H), 7.46 (m, 2H), 7.70 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 169.9, 169.9, 156.1, 144.2, 132.8, 129.9, 126.1, 118.3, 113.5, 81.0, 75.5, 62.3, 14.1. HRMS: Calcd for $C_{13}H_{12}N_2O_5$ 244.0848, found m/e (M^+) 244.0848; **3f**: The ^{1}H NMR compared favorably with that reported in *Liebigs Ann. Chem.* **1972**, *763*, 1; **3g**: ^{1}H NMR ($CDCl_3$): δ 1.355 (t, 3H), 3.09 (s, 3H), 4.32 (dq, 2H), 4.58 (dd, 1H), 5.79 (d, 1H), 7.18 (d, 1H), 7.57 (d, 2H), 7.99 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 169.9, 156.1, 145.1, 140.7, 128.1, 126.3, 80.9, 75.5, 62.2, 44.4, 14.1. HRMS: Calcd for $C_{13}H_{15}NO_5S$ 297.0671, found m/e (M^+) 297.0671; **3h**: ^{1}H NMR ($CDCl_3$): δ 1.30 (m, 6H), 2.29 (s, 3H), 4.26 (m, 2H), 4.54 (d, 1H), 5.90 (d, 1H), 7.03 (overlapping area, 3H), 7.12 (d, 1H). ^{13}C NMR ($CDCl_3$): δ 170.6, 156.6, 136.7, 136.2, 131.9, 130.8, 129.3, 125.9, 79.9, 75.0, 61.9, 21.0, 18.7, 14.2. HRMS: Calcd for $C_{14}H_{17}NO_3$ 247.1208, found m/e (M^+) 247.1211; **3i**: ^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3H), 3.77 and 3.76 (two s, 6H), 4.29 (dq, 2H), 4.48 (dd, 1H), 5.88 (d, 1H), 6.83 (d, 2H), 6.87 (s, 1H), 7.07 (d, 1H). ^{13}C NMR ($CDCl_3$): δ 170.9, 156.1, 153.7, 150.2, 128.2, 113.7, 112.3, 111.6, 79.1, 74.8, 61.7, 55.8, 14.2. HRMS: Calcd for $C_{14}H_{17}NO_5$ 279.1107, found m/e (M^+) 279.1107; **3k**: ^{1}H NMR ($CDCl_3$): δ 0.93 (s, 9H), 1.31 (t, 3H), 4.24 (q, 2H), 4.39 (s, 2H), 6.95 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 171.3, 156.7, 89.1, 68.2, 61.6, 33.7, 24.5, 14.1. HRMS: Calcd for $C_{10}H_{17}NO_5$ 199.1208, found m/e (M^+) 199.1209; **3o**: On the basis of the ^{1}H NMR spectrum, this known compound contained an inseparable 8% of the corresponding Knoevenagel by-product. Because no NMR spectra have been reported for **3o**, we report them here. ^{1}H NMR of **3o** ($CDCl_3$): δ 1.33 (t, 3H), 3.79 (s, 3H), 4.29 (q, 2H), 4.51

(dd, 1H), 5.91 (d, 1H), 6.89 (d, 1H), 6.96 (s, 1H), 7.08 (d, 1H), 7.32–7.27 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 171.0, 156.3, 156.2, 129.7, 127.1, 126.2, 120.7, 110.6, 79.4, 74.7, 61.7, 55.3, 14.3; **3p**: ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3H), 4.30 (q, 2H), 4.69 (dd, 1H), 5.85 (d, 1H), 7.16 (d, 1H), 7.37 (dd, 1H), 7.49 (m, 2H), 7.83 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 170.5, 156.4, 136.1, 133.3, 129.2, 128.1, 127.8, 126.7, 126.6, 125.1, 122.8, 82.4, 75.4, 62.0, 14.1. HRMS: Calcd for $C_{16}H_{15}NO_3$ 269.1052, found m/e (M^+) 269.1052; **2q**: The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1990**, *55*, 1649.