Piperidine Promoted Aldol Reaction of Alkynyl Aldehydes and Ethyl Diazoacetate

Guifu Zhang, Sheng Sun, Longqiang Jiang, Shaofa Sun, Xing Luo, Zhi Chen, Haibing Guo, Yalan Xing

PII: S0040-4039(17)30001-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.01.001
Reference: TETL 48504

To appear in: *Tetrahedron Letters*

Received Date: 15 December 2016
Accepted Date: 2 January 2017

Please cite this article as: Zhang, G., Sun, S., Jiang, L., Sun, S., Luo, X., Chen, Z., Guo, H., Xing, Y., Piperidine Promoted Aldol Reaction of Alkynyl Aldehydes and Ethyl Diazoacetate, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.01.001

Piperidine Promoted Aldol Reaction of Alkynyl Aldehydes and Ethyl Diazoacetate

Guifu Zhang,[a,†] Sheng Sun,[a,†] Longqiang Jiang,[a] Shaofa Sun,*[,a] Xing Luo,[a] Zhi Chen,[a] Haibing Guo,[a] and Yalan Xing*[,b]

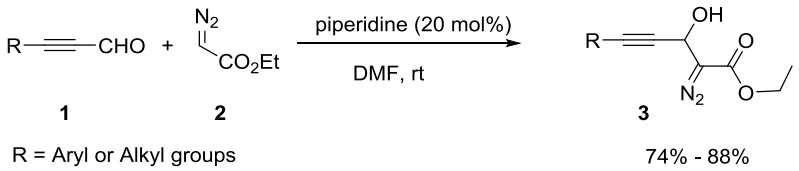
[a]Non-power Nuclear Technology Collaborative Innovation Center, School of Nuclear Technology and Chemistry & Life Science, Hubei University of Science and Technology, Xianning 437100, China.

[b]Department of Chemistry, William Paterson University, 300 Pompton Rd, Wayne, NJ 07470, US

†These authors contributed equally to the work.

**E-mail: sunshaofa@mail.hbust.com.cn, xingy@wpunj.edu*

Graphic abstract



Highlights

- Efficient synthesis of complex diazo compounds containing propargyl alcohol
- Aldol reaction of alkynyl aldehydes and ethyl diazoacetate
- Easy operation, ambient temperature, good yields
- Broad functional group tolerance

Keywords:

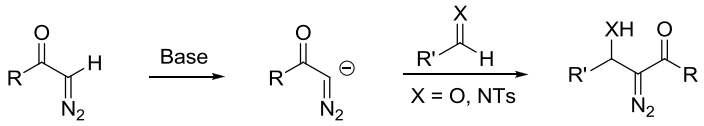
Aldol reaction, piperidine, diazoacetate, alkynyl aldehyde

Abstract

Complex diazo compounds containing propargyl alcohol functional group were prepared by an efficient aldol reaction of alkynyl aldehydes and ethyl diazoacetate in good yields. Piperidine was utilized as a base to catalyze this transformation. The aldol reaction showed broad substrate scopes and good functional group compatibility.

Introduction

α-Diazocarbonyl compounds have been extensively utilized in organic synthesis because they can undergo a wide variety of useful tranformations under mild reaction conditions.[1] For example, α-Diazocarbonyl compounds are widely used as nucleophiles when treated with base to prepare complex diazo compounds (Scheme 1). A base promoted deprotonation of acyl diazomethane generates an anion bearing a diazo group. This anion is highly reactive and readily react with C=O or C=N bonds to provide nucleophilic addition products.

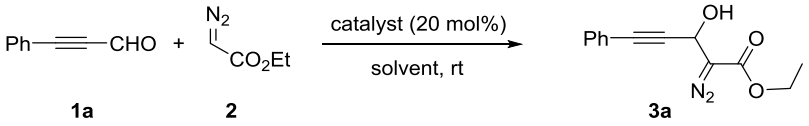


Scheme 1. Nucleophilic Addition of α-diazocarbonyl Anion

We are interested in developing a catalytic reaction for the preparation of complex diazo compounds from nucleophilic addition reaction of α-diazocarbonyl anion and alkynyl aldehydes. Generation of α-diazocarbonyl anion is usually achieved by the treatment of α-diazoketone or α-diazocarbonyl ester with a base, for instance, BuLi,[2] LDA,[3] NaH,[4] and KOH,[5] etc. These bases are generally very strong and require harsh reaction condition. DBU as a mild base was reported to deprotonate α-diazocarbonyl,[6] however, this reaction need to be operated under inert atmosphere. Herein, we present our results of an efficient, labile, and robust aldol reaction of α-diazocarbonyl anion and alkynyl aldehydes catalyzed by piperidine.

Results and Discussion

First, phenylpropiolaldehyde[7] **1a** was chosen as the model substrate to react with ethyl diazoacetate **2** for the investigation of the optimal reaction conditions. Piperidine was used as the base to screen the solvent effect. Many different solvents such as DMF, benzene, THF, toluene, CH_2Cl_2, MTBE (), CH_3OH (entry 1-8) were tested, and DMF was found to give the best yield of the aldol product **3a** (86%) in shortest reaction time (6h). Next, we explored different base catalysts using DMF as the optimal solvent. Organic bases such DBU, TEA, D-Porline and pyrolidine (entry 9-12) all provided the desired product in decent yield but not as high and efficient as piperidine. Unfortunately, when inorganic bases such as NaOH and $CsCO_3$ (entry 13 and 14) were utilized as base catalysts, no desired product was observed. In addition, the reaction failed to generate the desired products when no catalyst was employed (entry8).



Entry[a]	Catalyst	Solvent	T	Yield[b]
1	Piperidine	DMF	6h	86%
2	Piperidine	benzene	10h	56%
3	Piperidine	THF	10h	73%
4	Piperidine	toluene	12h	60%
5	Piperidine	CH_2Cl_2	14h	50%
6	Piperidine	MTBE	18h	53%
7	Piperidine	CH_3OH	18h	48%.
8	None	DMF	18h	n.r.
9	DBU	DMF	14h	62%
10	TEA	DMF	14h	63%
11	D-Proline	DMF	12h	50%

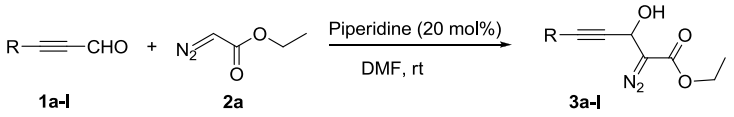
12	pyrolidine	DMF	12h	75%
13	NaOH	DMF	10h	n.r
14	Cs_2CO_3	DMF	12h	n.r

[a] Reaction conditions: a mixture of **1a** (1.0 mmol), 2 (1.1 mmol), catalyst (0.2 mmol), in solvent (2 mL) were stirred at room temperature for a certain period of time.

[b] Yield of isolated product.

Table 1. Optimization of the Aldol Reaction

With the optimal condition in hand, we next turned our attention to explore the substrate scopes and limitations of alkynyl aldehyde reaction partner (Table 2). It was found that aryl alkynyl aldehyde provided the aldol products in good to moderate yields (product 3a-3g). Electron withdrawing groups such as fluorine and electron donating groups such as methoxyl, methyl, ethyl and t-butyl groups on the aromatic ring did not affect the reaction yields. Heterocyclic aromatic ring such as thiophene and pyridine also gave good yield (74% and 76%) of the desired product. When alkyl alkynyl aldehydes were used in this Aldol reaction, the reaction also provided good yield for the desired products (3k and 3l).



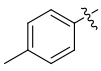
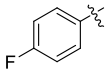
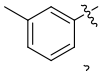
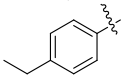
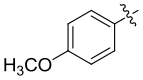
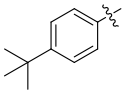
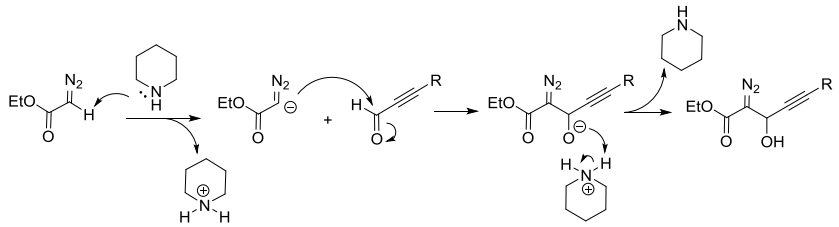
Entry	R	Yield(%)	Entry	R	Yield(%)
3a		86	3g		88
3b		82	3h		86
3c		80	3i		74
3d		85	3j		76
3e		80	3k		77
3f		81	3l		80

Table 2 Scope of Aldehyde

This reaction is an aldol type of nucleophilic addition reaction. First, piperidine serves as a mild base to deprotonate the ethyl diazoacetate to generate the α-acyldiazo anion. The resulting anion adds to the alkynyl aldehyde to generate the alkoxide ion which then gets protonated to produce the alcohol product containing diazo group.



Scheme 2. Reaction Mechanism

Conclusion

In summary, a highly efficient piperidine catalyzed aldol reaction of alkynyl aldehydes and ethyl diazoacetates was developed. The Aldol reaction afforded the diazo componds contain a progargyl alcohol functional group at room temperature in good yields under mild reaction conditions and short reaction time. Akynyl aldehydes showed broad substrate scopes and good functional group compatibility. Further extension of this efficient synthetic strategy and its application is under way in our laboratory and will be presented in due course.

Acknowledgement

The authors are grateful to the National Natural Science Foundation of China (NSFC-21202136). The authors are also grateful to National Natural Science Foundation (21602053). This research was supported (in part) by a grant from the Center for Research, College of Science and Health, William Paterson University of New Jersey.

References

[1] a) Nitrile oxides, nitrones and nitronates in organic synthesis, Henry Feuer, Ed.; Wiley: New York, 2007. b) Ye, T.; McKervey M. A. *Chem. Rev*. **1994**, *94*, 1091. c) Heaney, F. *Eur. J. Org. Chem.* **2012**, 3043

[2] (a) Schollkopf, U.; Frasnelli, H.; Hoppe, D. *Angew. Chem., Int. Ed.* **1970**, 9, 300; (b) Schollkopf, U.; Banhidai, B.; Frasnelli, H.;
Meyer, R.; Beckhaus, H. *Liebigs Ann. Chem.* **1974**, 1767.

[3] (a) Pellicciari, R.; Natalini, B. *J. Chem. Soc., Perkin Trans.*1 **1977**, 1882; (b) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. *J. Am. Chem. Soc.* **1996**, 118, 1; (c) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett*. **1987**, 28, 5351.

[4] Jiang, N.; Qu, Z.; Wang, J. *Org. Lett*. **2001**, 3, 2989.

[5] (a) Wenkert, E.; McPherson, A. A. *J. Am. Chem. Soc*. **1972**, 94, 8084; (b) Burkoth, T. L. *Tetrahedron Lett*. **1969**, 57, 5049; (c) Woolsey, N. F.; Khalil, M. H. *J. Org. Chem.* **1972**, 37, 2405.

[6] Jiang, N.; Wang, J. *Tetrahedron Lett*. **2002**, *43*, 1285

[7] Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, 39, 6427-6428.