Green synthesis of ethyl oxalate benzylidinyl hydrazides

Zhi Xiang Zhao, Li Ping Cheng, Wan Pang

PII: S0040-4039(18)30517-3
DOI: https://doi.org/10.1016/j.tetlet.2018.04.047
Reference: TETL 49910

To appear in: *Tetrahedron Letters*

Received Date: 7 March 2018
Revised Date: 13 April 2018
Accepted Date: 18 April 2018

Please cite this article as: Zhao, Z.X., Cheng, L.P., Pang, W., Green synthesis of ethyl oxalate benzylidinyl hydrazides, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.04.047

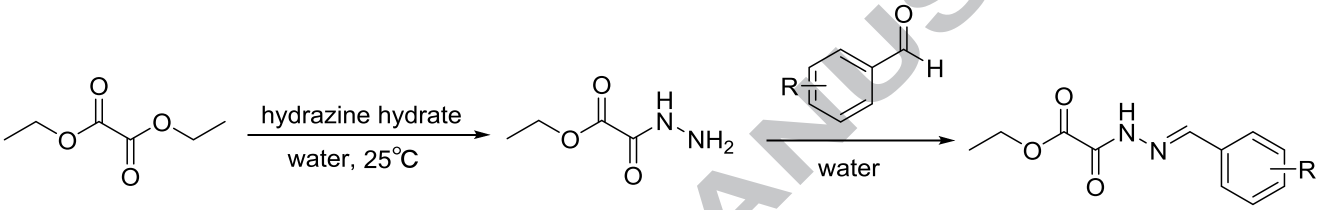
Graphical Abstract

The ethyl oxalate benzylidinyl hydrazides could be easily obtained by the reaction of benzaldehyde derivatives with monoethyl oxalate hydrazide in water.

Green synthesis of ethyl oxalate benzylidinyl hydrazides

Zhi Xiang Zhao[a] , Li Ping Cheng[a,] ∗ and Wan Pang[a,] ∗

[a]*School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, China*



Tetrahedron Letters
journal homepage: www.elsevier.com

Green synthesis of ethyl oxalate benzylidinyl hydrazides

Zhi Xiang Zhao[a] , Li Ping Cheng[a, ∗] and Wan Pang[a, ∗]

[a]School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Acylhydrazone compounds
green synthesis
Schiff-base

ABSTRACT

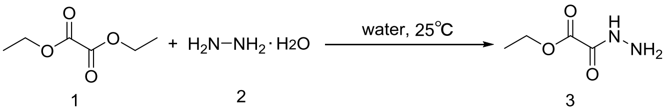
Acylhydrazone compounds play an important role in medicine, materials and other fields. Herein we report the synthesis of ethyl oxalate benzylidinyl hydrazides by the reaction of benzaldehyde derivatives and ethyl oxalate hydrazide under catalyst-free conditions in H_2O near room temperature. This green synthesis method has the advantages of mild reaction conditions, fast reaction rate, non-catalytic, good yield and easy isolation. These synthesized ethyl oxalate benzylidinyl hydrazides can be used as Schiff base metal complexes of small molecule ligands.

Schiff-bases were reported with applications in various areas, such as medicine, catalysis and materials[1-3]. They play important roles in industrial products of human life. Therefore, synthesis of Schiff-bases in a green way is very important. The green chemistry idea is to increase production, reduce environmental pollution and simplify the reaction process[4]. Green chemistry inspires us to explore a new method to prepare Schiff-bases.

Acylhydrazones are a class of Schiff-base with the special structure of —CO—NH—N=C—. Due to this construction, they have quiet a few advantages that ordinary Schiff-bases don't have[5]. Furthermore, acylhydrazone compounds had widespread applications in fields of materials, drugs, catalysis, and molecular electronics, etc[6-10]. Imine synthesis is one of the most useful tools to build Schiff base molecules. Traditional methods for the synthesis of acylhydrazones often used organic solvents. For example, Maccioni et al.[11] synthesized a few N-arylidenearyl-hydrazides in 2-propanol. The reaction was carried out under reflux with heating. Wang et al.[12] synthesized 4-hydroxy-3-methoxy-benzaldehyde series of aroyl hydrazones in ethanol and heated at 95 °C for 6 h-9 h[13]. These synthesis methods required not only the presence of organic solvents but also longer reaction time. The present study developed a simple, green and catalyst-free method for the synthesis of a series of ethyl oxalate benzylidinyl hydrazides. They could be easily obtained by the reaction of benzaldehyde derivatives with ethyl oxalate hydrazide. Most important of all, all reactions run in water.

We began our study with the commercially available diethyl oxalate **1** and hydrazine hydrate **2** (**Scheme 1**). According to previous reports of Braccio et al, compound **3** was prepared by the reaction of diethyl oxalate and hydrazine, the yield is 29%[14]. In this study, 2 equiv diethyl oxalate reacts with 1 equiv hydrazine hydrate in water under room temperature conditions stirred for overnight. Then, The aqueous solution was extracted with ethyl acetate, organic phases containing excessive diethyl oxalate were discarded and the aqueous of ethyl oxalate hydrazide were collected. Compound **3** can be stored in aqueous solution.

We initially envisioned the synthesis of ethyl oxalate 2-methoxy-benzylidinyl hydrazide **5a**. It is delightful that a white crystal was obtained by treating 2-methoxybenzaldehyde with ethyl oxalate hydrazide stirred for 7h in aqueous, the yield is 77.8%. Encouraged by this result, several other benzaldehyde derivatives were subsequently explored for the reaction (**Table 1**).



Scheme 1. Preparation of the compound monoethyl oxalate hydrazide **3**.

Various benzaldehyde derivatives were added to the aqueous solution of ethyl oxalate hydrazide **3** and the corresponding compounds **5a-5p** were obtained. The desired compound **5c** could be obtained with the yield 92.3% (**Table 1**). However, compounds **5b, 5d, 5e, 5i** were obtained in the same method, which resulted in reduced yields and needed longer reaction time

---

∗ Corresponding author. Tel.: +86-21-60873250; fax: +86-21-60877231; e-mail: chengliping@sit.edu.cn

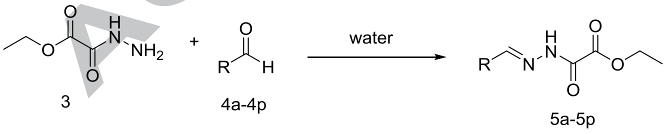
∗ Corresponding author. Tel.: +86-21-60873250; fax: +86-21-60877231; e-mail: pangwan@sit.edu.cn

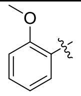
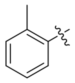
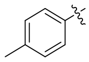
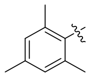
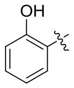
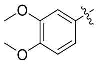
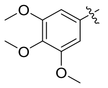
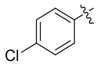
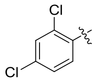
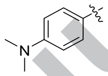
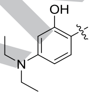
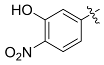
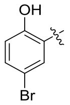
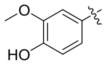
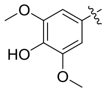
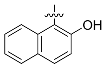
(**Table 1**). Perhaps ortho-substitutes weren't conducive to these reactions. These results led us to explore the reaction of more other ortho-substituted benzaldehyde derivatives with ethyl oxalate hydrazide. However, the yields of **5k, 5m** and **5p** are high even though the ortho substituent (-OH) is present in the phenyl ring. This phenomenon may be attributed to the electron withdrawing effect of hydroxyl, which may improve the reactivity of carbonyl group. It should be mentioned that compounds **5e**, **5k**, **5m**, **5p** with hydroxy substitutes at the ortho position of phenyl are a class of diprotic planar ONO tridentate chelating ligands. Such compounds are capable of forming stable complexes with diverse divalent metals[15-19]. Besides, the synthesis of ethyl oxalate benzylidinyl hydrazides was also explored by using of a variety of benzaldehyde derivatives without ortho steric hindrance. Satisfactorily, the reaction rate is quite fast and the yield is good (**5f**, **5g**, **5j**, **5l**, **5n**, **5o**).

To explore the influence of halogen substituents on the synthesis of ethyl oxalate benzylidinyl hydrazides, compounds **5h**, **5i**, and **5m** were synthesized. As shown in (**Table 1**), the reaction of 4-chlorobenzaldehyde **4h** with ethyl oxalate hydrazide led to compound **5h** in 72.2% yield at room temperature. Compound **5m** was obtained in high yield using the same method. But ortho chlorine benzaldehyde **5i** was difficult to react completely at room temperature. Exploration of the optimal reaction temperature with the synthesis of **5i**, it was obtained at 80 °C in moderate yield. In addition, the optimized reaction temperature for other compounds were also carried out. Compounds **5j**, **5k**, **5l**, and **5p** were more readily prepared from ethyl oxalate hydrazide **3** through reaction with corresponding benzaldehyde derivatives **4j**, **4k**, **4l**, and **4p** at 60 ℃.

In summary, as observed in this study, the steric hindrance has an obvious influence on the reaction rate, while the electron effect has no significant effect on the reaction rate. The ethyl oxalate benzylidinyl hydrazides **5a-5p** were characterized using ^{1}H NMR, ^{13}C NMR, IR and FT-TR spectral data. The characteristic singlet at δ=8-9 ppm was ascribed to the -CH=N-. In the ^{13}C NMR spectra of the products **5a-p**, signals located around δ=146-153 ppm were due to the methylene carbon. The characteristic IR absorption peaks of -CH=N- can be found at 1592.74-1632.14 cm^{-1} in the infrared spectrum.

Table 1. The reaction of compound **3** and compound **4a-4p** in aqueous afford compound **5a-5p**.



Entry	R	Temp (°C)	Time (h/min）	Yield[a] (%)	Mp (°C)
5a		25	7 h	77.8	131-132
5b		25	70 min	76.9	142-143
5c		25	65 min	92.3	130-131
5d		25	2 h	68.5	142-144
5e		25	1 h	66.7	152-153
5f		25	10 min	98.0	159-160
5g		25	15 min	73.3	150-151
5h		25	5 h	72.2	152-153
5i		80	5 h	67.6	134-135
5j		60	30 min	76.2	148-149
5k		60	5 h	94.4	139-141
5l		60	40 min	71.4	178-180
5m		25	2 h	95.5	142-144
5n		25	30 min	88.4	190-192
5o		25	20 min	60.7	202-204
5p		60	3 h	90.0	178-180

[a] The yields were calculated relative to the aldehyde quantity.

In this study, we have designed and prepared a series of new ethyl oxalate benzylidinyl hydrazides **5a-5p** as the new Schiff base small molecule ligands. The synthesis methods for these compounds are simple and efficient. Most important of all, we used green and readily available water instead of traditional organic solvents in these reactions. Aromatic aldehydes without ortho steric hindrance were more reactive than those aromatic aldehydes with ortho steric hindrance. It is a useful reaction method for synthesis of ethyl oxalate benzylidinyl hydrazides.

Acknowledgments

Thanks for financial support given by Natural Science Foundation of Shanghai (No. 15ZR1440400), Collaborative Innovation Fund (No. XTCX2016-14), National Youth Fund Project of China (No. 21602135), Shanghai Municipal Education

Commission (Plateau Discipline Construction Program), and the National Natural Science Foundation of China (No. 21472126).

Supplementary Material

Experimentation, Mass spectra (MS), IR, 1H NMR, and 13C NMR spectra for all the ethyl oxalate benzylidinyl hydrazides can be found in the supplementary material.

References and notes

1. Desai, S. B.; Desai, P. B.; Desai, K. R.; *Hetercycl Common*., **2001**, 7(1), 83-90.
2. Bastos, M. B. R.; Moreira, J. C.; Farias, P. A. M.; *Analytica Chimica Acta*. **2000**, 408, 83-88.
3. Segura, JoséL.; Manchenõ, María J.; Zamora Félix.Chem. Soc. Rev. **2016**, 45, 5635.
4. Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green. Chem*. **2004**, 6, 128.
5. Mladenka, P.; Kalinowski, D. S.; Haskova, P.; Bobrovova, Z.; Hrdina, R.; Simunek, T.; Nachtigal, P.; Semecky, V.; Vavrova, J.; Holeckova, M.; Palicka, V.; Mazurova, Y.; Jansson P. J.; Richardson, D. R. Chem. Res. Toxicol., **2009**, 22, 208–217.
6. Xin, Y.; Yuan, J. Y. *Polym. Chem.*, **2012**, 3, 3045.
7. Zheng, Y. W.; Ren, J.; Wu, Y. Q.; Meng, X. T.; Zhao, Y. B.; Wu, C. L.; *Bioconjugate Chem*. **2017**, 28, 2620−2626.
8. Xu, L. M.; Jiang, L. X.; Drechsler, M.; Sun, Y.; Liu, Z. R.; Huang, J. B.; Tang, B. Z.; Li, Z. B.; Martien A. Stuart, C.; Yan, Y. *J. Am. Chem. Soc*. **2014**, 136, 1942−1947.
9. William, O. G.; Leonard J. Barbour, jerry L. Atwood. *Science* **1999**, 285, 1049−1052.
10. Ge, Z. S.; Liu. S. Y.; *Chem. Soc.Rev*. **2013**, 42, 7289−7325.
11. Maccioni, E.; Alcaro, S.; Cirilli, R.; Vigo, S.; Cardia, M. C.; Sanna, M. L.; Meleddu, R.; Yanez, M.; Costa, G.; Casu, L.; Matyus, P.; Distinto. S. *J. Med. Chem.* **2011**, 54, 6394–6398.
12. Wang, L.; Guo, D. G.; Wang, Y. Y.; Zheng, C. Z. *RSC Adv*. **2014**, 4, 58895–58901.
13. Iskander, M. F.; EI-Aggan, A. M.; Refaat, L. S.; Sayed, L. E.; *Inorg. Chim. Acta* 14, **1975**, 167–172.
14. Braccio, M. D.; Grossi, G.; Roma, G.; Piras, D.; Mattioli, F.; Gosmar. M.; *European Journal of Medicinal Chemistry* 43, **2008**, 584-594.
15. Iskander, M. F.; Sayed, L. E.; Saddeck, S.; Abuo-Taleb, M. A. *Trans. Met. Chem.* 5, **1980**, 168–172.
16. Iskander, Magdi F.; Khalil, Tarek E.; Foro, Sabine. *Inorganica Chimica Acta.* 453, **2016**, 633-646.
17. Chan, S.C.; Koh, L.L.; Leung, P.-H.; Ranford, J.D. Inorg. Chim. Acta. 236, **1995,** 101–108.
18. Ainscough, E.W.; Brodie, A.M.; Dobbs, A.J.; Ranford, J.D.; Waters, J.M.; *Inorg. Chim. Acta* 267, **1998**, 27–38.
19. Koh, L.L.; Kon, O.L.; Loh, K.W. *J. Inorg. Biochem*. 72 , **1998**, 155–162.

20.

Highlights

- A series of novel ethyl oxalate benzylidinyl hydrazide derivatives in water were synthesized.
- Our synthesis method was green, simple and efficient.
- This green reaction methods of ethyl oxalate benzylidinyl hydrazide have wide application prospects.