

无金属条件下的酰胺脱水反应

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摘要

酰胺作为广泛存在于自然界与药物分子中的含氮化合物, 在工业, 医药, 农药等领域发挥了重要作用。因此, 酰胺反应的研究逐渐受到合成化学家的广泛关注。文献调研后, 本文对无金属条件下的酰胺脱水反应和无金属条件下的酰胺脱水重排反应进行了总结和探讨, 并对该脱水反应的发展做出展望。

关键词

酰胺, 脱水反应, 脱水重排

Dehydration of Amides under Nonmetallic Conditions

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Abstract

Amides are widely existing in nature, and drug molecules play an important role in the industry, medicine, pesticides and other fields. Therefore, the study of amides has gradually attracted the attention of synthetic chemists. After a literature review, this paper summarizes and discusses the dehydration and rearrangement of amides under metal-free conditions and looks forward to the development of this dehydration reaction.

Keywords

Amide, Dehydration Reaction, Dehydration Rearrangement

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1. 引言

酰胺是一类重要的有机化合物，广泛存在于多种具有生物活性的药物中间体、天然产物以及多种聚合物材料中。如聚酰胺、色素和染料、药物、农用化学品等[1]。一直以来关于酰胺反应的研究都被研究人员广泛关注，其中，以金属催化的形式进行的酰胺脱水反应在近几十年得到了巨大发展[2]-[12]，但该类方法普遍存在反应条件苛刻、原材料昂贵且制备过程繁琐、易导致重金属污染等问题。相比之下，无金属条件下的酰胺脱水反应具有非常大的研究价值。本文将对无金属条件下的酰胺脱水反应的研究进展进行总结和探讨，重点分为无金属条件下的酰胺脱水成腈及无金属条件下的酰胺脱水重排两个部分。

2. 无金属条件下的酰胺脱水成腈

2.1. 无金属条件下酰胺脱水剂脱水

早在 1892 年 Pinner 等人[13]就发现一些腈可能可以通过乙酰氯或苯甲酰氯与酰胺的作用来制备腈。而在 1945 年 Mitchell 等人[14]对酰胺进行定量分析时发现伯酰胺与 3,5-二硝基苯甲酰氯反应可形成腈(图 1)。1951 年 Thompson 等人[15]在对酰胺进行二酰化的过程中同样发现，强羧酸的卤化物会使酰胺脱水形成腈，但并未进行具体报道。

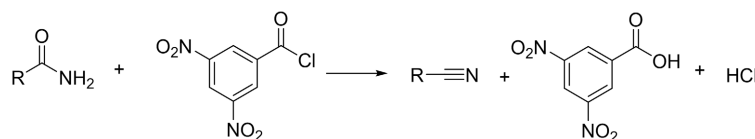
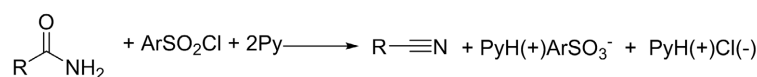


Figure 1. The unsubstituted amide reacts quantitatively with 3,5-dinitrobenzoyl chloride to form nitrile

图 1. 伯酰胺与 3,5-二硝基苯甲酰氯发生定量反应形成腈

直到 1954 年 Pilgrim 等人[16]才首次报道，芳基磺酰卤化物-吡啶混合物在温和条件下可将伯酰胺转化为腈(图 2)。



Py=pyridine

Figure 2. Arylsulfonyl halide pyridine dehydration of amide to nitrile

图 2. 芳基磺酰卤化物-吡啶将酰胺脱水成腈

1970 年 Dennis 等人[17]报道了以硅烷、氯硅烷、烷氧基硅烷和氨基硅烷为脱水试剂对酰胺进行脱水。反应在轻度碱性、中性或酸性条件下都可以顺利进行，且腈易于分离(图 3)。但取代酰胺如 N-甲基苯甲酰胺及乙酰胺产率分别只有 43% 和 27%，这些反应通常需要加热到 200°C 以上才能反应。

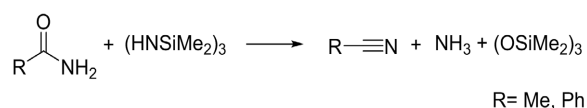


Figure 3. Benzoamide or acetamide is reacted at 180~200°C to obtain benzonitrile or acetonitrile

图 3. 苯甲酰胺或乙酰胺在 180~200°C 下反应得到苯甲腈或乙腈

Casini 课题组[18]在 1977 年发现 1,2,3-茛三酮与 α -酸化化合物形成加合物脱水的过程中发现, 三氟乙酸酐可以很容易将伯酰胺转化成腈(图 4)。

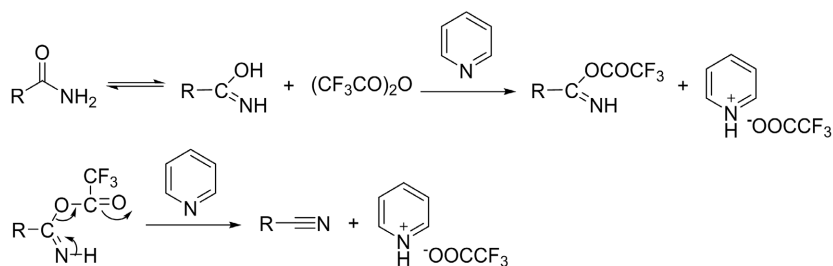


Figure 4. Trifluoroacetic anhydride as dehydrating agent for amide dehydration

图 4. 三氟乙酸酐作为脱水剂对酰胺脱水

2006 年, Shia 课题组[19]利用二氯磷酸酯/DBU 为温和脱水剂, 开发了一种操作简单、高产率的将伯酰胺转化为相应的腈的方法(图 5)。这种新开发的方法具有广泛的合成用途, 特别是用于制备热力学不稳定的腈。

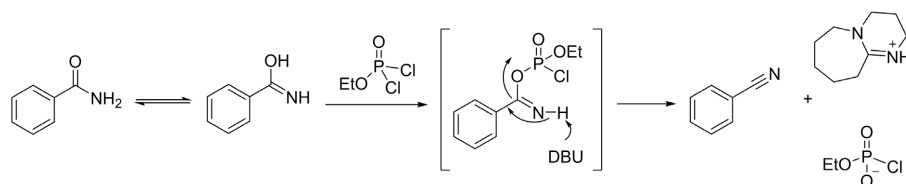


Figure 5. Ethyl dichlorophosphate/DBU as dehydrating agent

图 5. 二氯磷酸酯/DBU 脱水剂脱水

2011 年, Unnikrishnan 等人[20]发现 Burgess reagent (伯吉斯试剂)可以使酰胺在回流的条件下脱水形成腈(图 6)。原料易于制备(Burgess reagent 目前已是商用试剂), 为酰胺类化合物脱水反应提供了一条新路径。

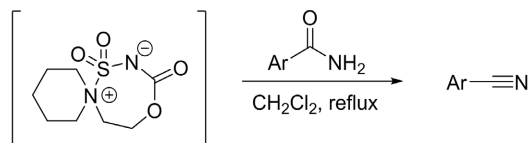


Figure 6. Burgess reagent as dehydrating agent

图 6. 伯吉斯试剂脱水成腈

2.2. 无金属有机催化的酰胺脱水

1996 年 Mioskowski 课题组[21]报道了醛催化水转移将伯酰胺转化为相应的腈的方法(图 7)。与以前

报道的方法相比, 该方法不需要强脱水或复杂的试剂, 并且反应底物范围广泛。

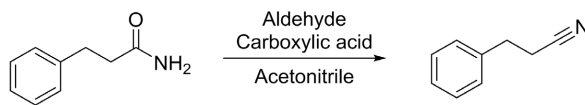


Figure 7. Aldehyde catalyzed water transfer converts primary aromatic amides to corresponding nitriles

图 7. 醛催化水转移将伯酰胺转化为相应的腈

Beller 等人于 2009 年[22]提出了一种在催化量氟(TBAF)的作用下, 用硅烷对芳香族和脂肪族酰胺进行脱水的方法(图 8)。与以往的不易制备的脱水试剂相比, 该方法使用的是商用试剂, 反应易于处理且对环境友好。值得注意的是, 脂肪族腈和芳香族腈的合成在该方法温和的条件下具有较高的选择性。

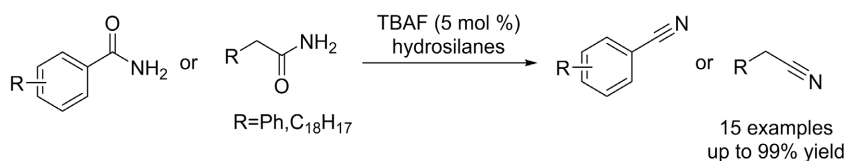


Figure 8. Dehydration of amide to nitrile catalyzed by fluorine

图 8. 氟催化脱水成腈

2018 年, Malkov 等人[23]开发了一种 *appel* 型酰胺脱水成腈的高效方法。该方法以 1 mol% 的三苯基氧磷为催化剂, 在 10 min 以内即可完成。与 *appel* 反应相比, 该方法用草酰氯代替了对肾脏有毒的四氯化碳, 并且催化量的三苯基氧磷使得反应产物易于分离。同年, Sun 课题组[24]亦受到 *appel* 反应的启示, 发现在三乙胺的存在下, 用催化量的二甲亚砜可以将伯酰胺脱水形成腈(图 9), 为初级酰胺或醛酰胺脱水制备腈提供了一种实用的替代方法。

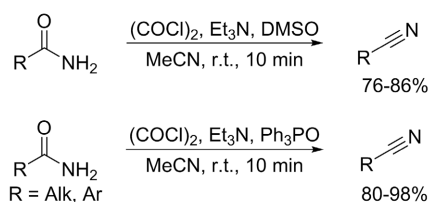


Figure 9. Dehydration of amide catalyzed by tri-phenylphosphine oxide and dimethyl sulfoxide

图 9. 三苯基氧磷和二甲亚砜催化酰胺脱水

2019 年, Manda 课题组[25]报道了第一个无金属催化硅烷作用下的伯酰胺在室温下脱水成腈的方法(图 10)。证明了 α -NHC 可以作为一种伯酰胺脱水反应的高效无金属催化剂。通过 DFT 计算, 反应通过低能垒的 β -消除得到相应的腈, 因而具有广泛的底物适用范围。

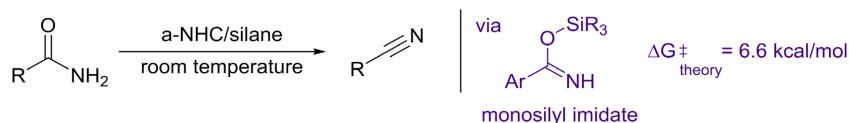


Figure 10. Dehydration of amide catalyzed by NHC

图 10. NHC 催化酰胺脱水

3. 无金属酰胺脱水重排

Brannock 等人于 1965 年[26]首次报道酰胺重排成腈的方法(图 11), 重排将 N-烯丙基酰胺转化为烯丙基腈。他们假定 N-烯丙基烯酮亚胺作为中间产物, 并提出这种重排过程可能是 3-aza-Claisen 反应的一个例子。与相似的[3,3]- σ 重排反应[27] [28] [29]相比, Brannock 的反应条件更加温和。

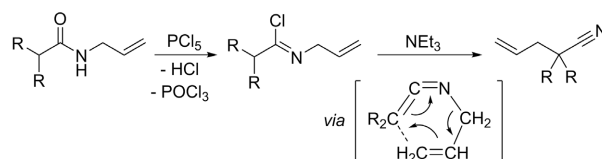


Figure 11. Rearrangement of N-allyl amide to allyl nitrile

图 11. N-烯丙基酰胺重排为烯丙基腈

1991 年 Walters 等人[30]受到 Brannock 的启发, 在 Brannock 反应的基础上进行进一步的研究, 开发了一种非常温和的 3-aza-Claisen 反应, N-烯丙基酰胺在室温中性条件下转化为中等到良好产率的戊烯基腈(图 12)。

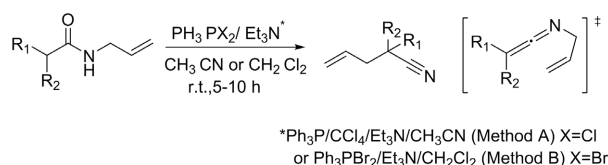


Figure 12. Mild 3-aza-Claisen reaction

图 12. 温和的 3-氮杂-克莱森反应

1993 年 Walters [31]对 N-烯丙基酰胺重排方法进行了探索(图 13)。以简单的 N-烯丙基酰胺为底物重排形成戊烯基腈为基础, 探索该反应方法的灵活性, 总结出了以下合成方法。


Rearrangement Conditions ^a	yield of Nitrile 4
1. 2 PPh ₃ , 2 CCl ₄ , 3 Et ₃ N	97%
2. 2 PPh ₃ , 2 CBr ₄ , 3 Et ₃ N	66%
3. PPh ₃ , I ₂ , 2 Et ₃ N	56%
4. Br ₂ •PPh ₃ , 2 Et ₃ N	89%
5. 3 I ₂ , 3 P(OEt) ₃ , 3 Et ₃ N	86%
6. 3 I ₂ , 3 P(OMe) ₃ , 3 Et ₃ N	36%
7. Tf ₂ O, 2 (iPr) ₂ NEt	67%
8. Triphosgene(1/2), 2.5 Et ₃ N	RT 78%
	0 °C 85%
	-78 °C 40%
9. (COCl) ₂ , 2 Et ₃ N	31%
10. PhCH ₂ NEt ⁺ Cl ⁻ (0.3%), CHCl ₃ , 50% Na/H ₂ O	39%
11. TFAA, 2 Et ₃ N	b

^aNumerical indicate relative stoichiometry. These reaction are usually run in dichloromethane and at room temperature
^bProduct formed, yield not determined

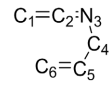
Figure 13. Reaction Conditions for the 3-aza-Claisen Rearrangement

图 13. 3-氮杂-克莱森重排的反应条件

1994年, Walters [32]对反应进行了计算(图 14), 过渡态结构的几何构型和能量计算表明烯酮亚胺的重排是一个非常放热的反应过程, 比起其它 3-aza-Claisen 变体, 烯酮亚胺过渡态结构更类似于初始材料。通过 MP4(SDTQ)/6-31G*/MP2/6-31G*对中性、带电分子以及假定的烯酮亚胺中间体进行理论计算, 为烯酮亚胺中间体的形成提供了有力支撑。



(1 neutral, 2 charged)



(3 Ketenimine)

structure	C ₁ C ₂	C ₁ C ₆	C ₂ X ₃	C ₄ X ₃	C ₄ C ₅	C ₅ C ₆
1. X = NH	1.392	2.072	1.363	1.806	1.416	1.393
2. X = NH ₂ ⁺	1.370	2.289	1.382	1.994	1.405	1.381
3	1.360	2.323	1.220	1.759	1.425	1.378

Figure 14. MP2/6-31G* Optimized Transition Structure Geometries for the Neutral (1). Charged (2), and Ketenimine (3) 3-Aza-Claisen

图 14. MP2/6-31G*优化中性的(1)带电的(2)和烯酮亚胺(3) 3-氮杂-共轭烯的过渡态的几何构型

4. 总结

本文系统介绍了在无金属条件下的酰胺脱水反应, 并从 1) 无金属条件下的酰胺脱水成腈; 2) 无金属条件下脱水重排两个方面介绍了反应的机理、底物适用范围、官能团兼容性问题。相比于金属催化的酰胺脱水体系, 无金属条件下的脱水反应的相关报道仍然较少, 因此, 该反应类型在酰胺脱水领域还有较大的发展空间。

参考文献

- [1] Jagadeesh, R.V., Junge, H. and Beller, M. (2014) Green Synthesis of Nitriles Using Non-Noble Metal Oxides-Based Nanocatalysts. *Nature Communications*, **5**, Article No. 4123. <https://doi.org/10.1038/ncomms5123>
- [2] Hanada, S., Motoyama Y. and Nagashima, H. (2008) Hydrosilanes Are Not Always Reducing Agents for Carbonyl Compounds but Can Also Induce Dehydration: A Ruthenium-Catalyzed Conversion of Primary Amides to Nitriles. *European Journal of Organic Chemistry*, **2008**, 4097-4100. <https://doi.org/10.1002/ejoc.200800523>
- [3] Zhou, S., Addis, D., Das, S., Junge, K. and Beller, M. (2009) New Catalytic Properties of Iron Complexes: Dehydration of Amides to Nitriles. *Chemical Communications*, **32**, 4883-4885. <https://doi.org/10.1039/b910145d>
- [4] Elangovan, S., Quintero-Duque, S., Dorcet, V., Roisnel, T., Norel, L., Darcel C. and Sortais, J.B. (2015) Knölker-Type Iron Complexes Bearing an N-Heterocyclic Carbene Ligand: Synthesis, Characterization, and Catalytic Dehydration of Primary Amides. *Organometallics*, **34**, 4521-4528. <https://doi.org/10.1021/acs.organomet.5b00553>
- [5] Yao, W., Fang, H., He, Q., Peng, D., Liu G. and Huang, Z. (2019) A BEt₃-Base Catalyst for Amide Reduction with Silane. *The Journal of Organic Chemistry*, **84**, 6084-6093. <https://doi.org/10.1021/acs.joc.9b00277>
- [6] Enthaler S. and Inoue, S. (2012) An Efficient Zinc-Catalyzed Dehydration of Primary Amides to Nitriles. *Chemistry - An Asian Journal*, **7**, 169-175. <https://doi.org/10.1002/asia.201100493>
- [7] Xue, B., Sun, H., Wang, Y., Zheng, T., Li, X., Fuhr O. and Fenske, D. (2016) Efficient Reductive Dehydration of Primary Amides to Nitriles Catalyzed by Hydrido Thiophenolato Iron(II) Complexes under Hydrosilation Conditions. *Catalysis Communications*, **86**, 148-150. <https://doi.org/10.1016/j.catcom.2016.08.024>
- [8] Enthaler, S. (2011) Straightforward Uranium-Catalyzed Dehydration of Primary Amides to Nitriles. *Chemistry*, **17**, 9316-9319. <https://doi.org/10.1002/chem.201101478>
- [9] Enthaler S. and Weidauer, M. (2011) Copper-Catalyzed Dehydration of Primary Amides to Nitriles. *Catalysis Letters*, **141**, 1079-1085. <https://doi.org/10.1007/s10562-011-0660-9>
- [10] Sueoka, S., Mitsudome, T., Mizugaki, T., Jitsukawa K. and Kaneda, K. (2010) Supported Monomeric Vanadium Catalyst for Dehydration of Amides to Form Nitriles. *Chemical Communications*, **46**, 8243-8245.

- <https://doi.org/10.1039/c0cc02412k>
- [11] Bézier, D., Venkanna, G. T., Sortais J.B. and Darcel, C. (2011) Well-Defined Cyclopentadienyl NHC Iron Complex as the Catalyst for Efficient Hydrosilylation of Amides to Amines and Nitriles. *ChemCatChem*, **3**, 1747-1750. <https://doi.org/10.1002/cctc.201100202>
- [12] Liu, R.Y., Bae, M. and Buchwald, S.L. (2018) Mechanistic Insight Facilitates Discovery of a Mild and Efficient Copper-Catalyzed Dehydration of Primary Amides to Nitriles Using Hydrosilanes. *Journal of the American Chemical Society*, **140**, 1627-1631. <https://doi.org/10.1021/jacs.8b00643>
- [13] Titherley, A.W. (1904) CLXIX.—The Acylation of Amides. *Journal of the Chemical Society, Transactions*, **85**, 1673-1691. <https://doi.org/10.1039/CT9048501673>
- [14] Mitchell, J. and Ashby, C.E. (1945) The Determination of Unsubstituted Acid Amides. *Journal of the American Chemical Society*, **67**, 161-164. <https://doi.org/10.1021/ja01218a003>
- [15] Thompson, Q.E. (1951) Preparation and Identification of N-Formylbenzamide and its Condensation Product with Phenylhydrazine. *Journal of the American Chemical Society*, **73**, 5914-5915. <https://doi.org/10.1021/ja01156a560>
- [16] Stephens, C.R., Bianco, E.J. and Pilgrim, F.J. (1955) A New Reagent for Dehydrating Primary Amides under Mild Conditions. *Journal of the American Chemical Society*, **77**, 1701-1702. <https://doi.org/10.1021/ja01611a102>
- [17] Dennis, W.E. (1970) Nitrile Synthesis. Dehydration of Amides by Silazanes, Chlorosilanes, Alkoxysilanes, and Aminosilanes. *The Journal of Organic Chemistry*, **35**, 3253-3255. <https://doi.org/10.1021/jo00835a016>
- [18] Campagna, F., Carotti A. and Casini, G. (1977) A Convenient Synthesis of Nitriles from Primary Amides under Mild Conditions. *Tetrahedron Letters*, **18**, 1813-1815. [https://doi.org/10.1016/S0040-4039\(01\)83612-1](https://doi.org/10.1016/S0040-4039(01)83612-1)
- [19] Kuo, C.W., Zhu, J.L., Wu, J.D., Chu, C.M., Yao C.F. and Shia, K.S. (2007) A Convenient New Procedure for Converting Primary Amides into Nitriles. *Chemical Communications*, No. 3, 301-303. <https://doi.org/10.1039/B614061K>
- [20] Rappai, J.P., Karthikeyan, J., Prathapan, S. and Unnikrishnan, P.A. (2011) Simple and Efficient One-Pot Synthesis of Nitriles from Amides and Oximes Using *in Situ*-Generated Burgess-Type Reagent. *Synthetic Communications*, **41**, 2601-2606. <https://doi.org/10.1080/00397911.2010.515333>
- [21] Heck, M.P., Wagner, A. and Mioskowski, C. (1996) Conversion of Primary Amides to Nitriles by Aldehyde-Catalyzed Water Transfer. *The Journal of Organic Chemistry*, **61**, 6486-6487. <https://doi.org/10.1021/jo961128v>
- [22] Zhou, S., Junge, K., Addis, D., Das, S. and Beller, M. (2009) A General and Convenient Catalytic Synthesis of Nitriles from Amides and Silanes. *Organic Letters*, **11**, 2461-2464. <https://doi.org/10.1021/ol900716q>
- [23] Shipilovskikh, S.A., Vaganov, V.Y., Denisova, E.I., Rubtsov, A.E. and Malkov, A.V. (2018) Dehydration of Amides to Nitriles under Conditions of a Catalytic Appel Reaction. *Organic Letters*, **20**, 728-731. <https://doi.org/10.1021/acs.orglett.7b03862>
- [24] Ding, R., Liu, Y., Han, M., Jiao, W., Li, J. Tian, H. and Sun, B. (2018) Synthesis of Nitriles from Primary Amides or Aldoximes under Conditions of a Catalytic Swern Oxidation. *The Journal of Organic Chemistry*, **83**, 12939-12944. <https://doi.org/10.1021/acs.joc.8b02190>
- [25] Hota, P.K., Maji, S., Ahmed, J., Rajendran, N.M. and Mandal, S.K. (2020) NHC-Catalyzed Silylative Dehydration of Primary Amides to Nitriles at Room Temperature. *Chemical Communications*, **56**, 575-578. <https://doi.org/10.1039/C9CC08413D>
- [26] Brannock, K.C. and Burpitt, R.D. (1965) The Preparation of 4-Pentenenitriles and 3,4-Pentadienenitriles from N-(2-Alkenyl)- and N-(2-Alkynyl)Amides. *The Journal of Organic Chemistry*, **30**, 2564-2565. <https://doi.org/10.1021/jo01019a016>
- [27] Tsunoda, T., Sakai, M., Sasaki, O., Sako, Y., Hondo Y. and Itô, S. (1992) Asymmetric Induction in Aza-Claisen Rearrangement of Carboxamide Enolates. Effect of Chiral Auxiliary on Nitrogen. *Tetrahedron Letters*, **33**, 1651-1654. [https://doi.org/10.1016/S0040-4039\(00\)91698-8](https://doi.org/10.1016/S0040-4039(00)91698-8)
- [28] Blechert, S. (1989) The Hetero-Cope Rearrangement in Organic Synthesis. *Synthesis*, **89**, 71-82. <https://doi.org/10.1055/s-1989-27158>
- [29] Ziegler, F.E. (1977) Stereo- and Regiochemistry of the Claisen Rearrangement: Applications to Natural Products Synthesis. *Accounts of Chemical Research*, **10**, 227-232. <https://doi.org/10.1021/ar50114a006>
- [30] Walters, M.A., McDonough, C.S., Brown P.S. and Hoem, A.B. (1991) An Extremely Mild 3-Aza-Claisen Reaction. 1. Rearrangement of Simple N-Allylamides. *Tetrahedron Letters*, **32**, 179-182. [https://doi.org/10.1016/0040-4039\(91\)80848-Z](https://doi.org/10.1016/0040-4039(91)80848-Z)
- [31] Walters, M.A., Hoem, A.B., Arcand, H.R., Hegeman, A.D. and McDonough, C.S. (1993) An Extremely Mild 3-Aza-Claisen Reaction. 2. New Conditions and the Rearrangement of α -Heteroatom Substituted Amides. *Tetrahedron Letters*, **34**, 1453-1456. [https://doi.org/10.1016/S0040-4039\(00\)60316-7](https://doi.org/10.1016/S0040-4039(00)60316-7)
- [32] Walters, M.A. (1994) *Ab Initio* Investigation of Three 3-Aza-Claisen Variations. *Journal of the American Chemical Society*, **116**, 11618-11619. <https://doi.org/10.1021/ja00104a072>