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A direct phosphine-mediated synthesis of polyfunctionalized pyrroles from arylglyoxals and β-enaminones

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ABSTRACT

An efficient one-pot reaction for the synthesis of pyrroles from β-enaminones and arylglyoxals is reported. This reaction, which is mediated by triphenylphosphine, eliminates triphenylphosphine oxide resulting in aromatization and has been employed to access a broad range of pyrrole derivatives.

Introduction

Nitrogen-containing five-membered heterocycles, such as pyrroles, are among the most important building blocks in organic chemistry. These heterocycles have found utility in various fields such as materials science, medicinal chemistry, polymer synthesis, and metal-coordinating ligands. Examples of these include diverse anti-inflammatory agents,[1] antitumor agents,[2–6] and they are generally utilized in cytotoxicity[7] and the treatment of hyperlipidemias.[8] Various methodologies have been developed for the synthesis of pyrroles.[9–11] Moreover, the application of multi-component reactions for the synthesis of pyrrole derivatives has been recently reviewed.[9] Multi-component reactions of arylglyoxals and enaminocarbonyls in the presence of various nucleophiles have recently been reported for the synthesis of poly-functionalized pyrroles.[12–14] However, to the best of our knowledge there are no reports on the condensation of β-enaminones[12,13] with arylglyoxals for the synthesis of pyrrole derivatives. In a continuation of our studies on the application of arylglyoxals for the synthesis of heterocyclic compounds,[15–17] herein, we report the condensation reaction between arylglyoxal monohydrates and enaminones in the presence of triphenylphosphine to afford substituted pyrroles in good yields.

Results and discussion

Initially, to investigate the reaction between arylglyoxals and enaminocarbonyls, *p*-chlorophenylglyoxal monohydrate was reacted with 4-phenylamino-3-pentene-2-one in acetonitrile. After 10 min of stirring, triphenylphosphine was added and the reaction progress was monitored by TLC. After 20 min of stirring at room temperature, the starting materials were consumed and two spots appeared on TLC, which were identified as pyrrole derivative **4a** and triphenylphosphine oxide. To investigate the generality of the reaction, different arylglyoxals were treated with enaminones and the related pyrrole derivatives were obtained in high yields (Table1). The enaminones of both aromatic and aliphatic amines reacted easily with arylglyoxals resulting in pyrrole derivatives, but the enaminones of ethyl acetoacetate led to complex mixtures and no pure product could be isolated (Scheme 1).

Structures of compounds **4a–m** were deduced from their spectral and analytical data. For example the ^{1}H NMR spectrum of **4a** exhibited two singlets at 2.43 and 2.51 ppm corresponding to the two methyl groups. The CH of the pyrrole ring was observed as a singlet at 6.74 ppm while the aromatic protons resonated between 6.97 and 7.50 ppm. The ^{13}C NMR spectrum of **4a** showed fifteen distinct signals which were consistent with the proposed structure; note the carbonyl resonance at 195.3 ppm. The structure of compound **4a** was also confirmed by IR spectroscopy exhibiting two absorption bands at 1549 cm^{-1} and 1659 cm^{-1} for the C=C and C=O groups, respectively.

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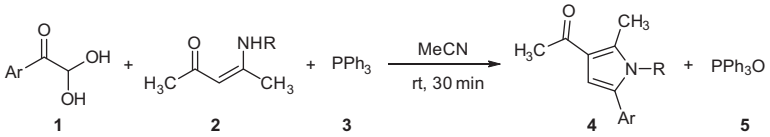
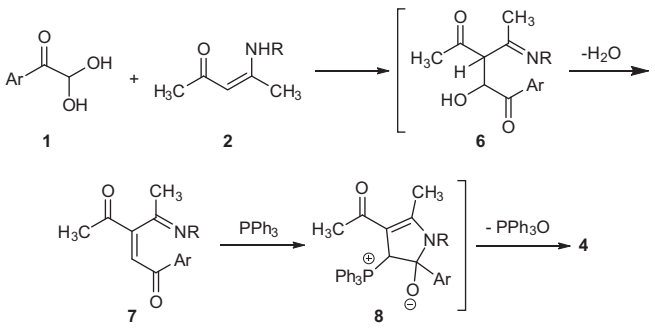
Table 1
Substrate scope

4	Ar	R	Yield[a] (%)
a	4-ClC_6H_4	C_6H_5	85
b	2-Naphthyl	C_6H_5	87
c	2-Naphthyl	4-ClC_6H_4	73
d	4-ClC_6H_4	4-ClC_6H_4	78
e	4-ClC_6H_4	4-$CH_3C_6H_4$	89
f	2-Naphthyl	4-$CH_3C_6H_4$	88
g	2-Naphthyl	4-$CH_3OC_6H_4CH_2$	92
h	4-FC_6H_4	C_6H_5	90
i	2-Naphthyl	4-$CH_3OC_6H_4$	93
j	4-FC_6H_4	4-$CH_3C_6H_4$	95
k	4-$CH_3C_6H_4$	$CH_2C_6H_5$	95
l	C_6H_5	*n*-Butyl	92
m	4-$CH_3C_6H_4$	*n*-Butyl	94

[a] Isolated yield. Conditions: MeCN, rt, 20 min.



Scheme 1. Reaction between arylglyoxals, β-enaminones, and triphenylphosphine.



Scheme 2. Proposed mechanism for the formation of pyrrole derivatives **4a**–**m**.

A proposed mechanism for formation of pyrrole derivatives **4a**–**m** is shown in Scheme 2. On the basis of the well-established regiochemistry of the addition of enaminones to arylglyoxals it is reasonable to assume that condensation of the arylglyoxal derivative at the aldehyde carbon with the enaminone derivatives affords intermediate **7**. Subsequent conjugate addition of triphenylphosphine to intermediate **7** affords the phosphonium betaine intermediate **8** which after elimination of triphenylphosphine oxide gives product **4**.

Conclusions

In summary, we report herein the reaction between β-enaminones and arylglyoxal monohydrates in the presence of triphenylphosphine to afford new pyrrole derivatives. The advantages of the method are readily available starting materials, neutral reaction conditions, and simple isolation and purification procedures for the products.

Supplementary data

Supplementary data (the experimental procedures and the IR, ^{1}H NMR, and ^{13}C NMR spectra of products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.075.

References and notes

1. (a) Wilkerson, W. W.; Copeland, A. R.; Covington, M.; Trzaskos, M. J. *J. Med. Chem.* **1996**, *38*, 3895; (b) Harrak, Y.; Rosell, G.; Daidone, G.; Plescia, S.; Schillaci, D.; Pujol, M. D. *Bioorg. Med. Chem.* **2007**, *15*, 4876; (c) Ushiyama, S.; Yamada, T.; Murakami, Y.; Kumakura, S.; Inoue, S.; Suzuki, K.; Nakao, A.; Kawara, A.; Kimura, T. *Eur. J. Pharmacol.* **2008**, *578*, 76.
2. (a) Arthur, R. C.; Gupton, T. J.; Kellogg, E. G.; Yeudall, W. A.; Cabot, C. M.; Newsham, I. F.; Gewirtz, A. D. *Biochem. Pharmacol.* **2007**, *74*, 981; (b) Kumar, R.; Lown, J. W. *Eur. J. Med. Chem.* **2005**, *40*, 641; (c) Bailly, C. *Curr. Med. Chem.* **2004**, *4*, 363; For the general biological activity of pyrroles, see: (d) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213.
3. Burnham, B. S.; Gupton, J. T.; Krumpe, K. E.; Webb, T.; Shuford, J.; Bowers, B.; Warren, A. E.; Barnes, C.; Hall, I. H. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 337.
4. Gupton, J. T.; Burnham, B. S.; Byrd, B. D.; Krumpe, K. E.; Stokes, C.; Shuford, J.; Winkle, S.; Webb, T.; Warren, A. E.; Barnes, C.; Henry, J.; Hall, I. H. *Pharmazie* **1999**, *54*, 691.
5. Krowicki, K.; Balzarini, T. J.; Clercq, E. D.; Newman, Robert A.; Lawn, J. William *J. Med. Chem.* **1988**, *31*, 341.
6. Dannhardt, G.; Kiefer, W.; Kramer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. *Eur. J. Med. Chem.* **2000**, *35*, 499.
7. Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619.
8. Justin, M. H.; O'Toole-Colin, K.; Getzel, A.; Argenti, A.; Michael, A. *Molecules* **2004**, *9*, 135.
9. Estévez, V.; Villacamp, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633.
10. Jones, R. A. In *Pyrroles, Part II: The Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles*; Wiley: New York, 1992.
11. Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.
12. Jiang, B.; Li, Q. Y.; Zhang, H.; Tu, S. J.; Pindi, S.; Li, G. *Org. Lett.* **2012**, *14*, 700.
13. Jiang, B.; Yi, M. S.; Shi, F.; Tu, S. J.; Pindi, S.; McDowell, P.; Li, G. *Chem. Commun.* **2012**, 808.
14. Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013**, *113*, 2958.
15. Anary-Abbasinejad, M.; Talebizadeh, M. *J. Iran Chem. Soc.* **2014**, *11*, 963.
16. Masoudi, M.; Anary-Abbasinejad, M. *J. Chem. Res.* **2015**, 145.
17. Anary-Abbasinejad, M.; Falahati, A. *J. Iran Chem. Soc.* **2015**. http://dx.doi.org/10.1007/s13738-015-0608-x. in press.