Tetrahedron Letters 53 (2012) 6710–6713

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of α-aryl enaminones through reactions of β-aryl enones with benzyl azide

Silvio Cunha *, Amenson Trindade Gomes

Instituto de Química, Universidade Federal da Bahia, Campus de Ondina, 40170-290 Salvador, BA, Brazil
Instituto Nacional de Ciência e Tecnologia – INCT em Energia e Ambiente, Universidade Federal da Bahia, Campus de Ondina, 40170-290 Salvador, BA, Brazil

ARTICLE INFO

Article history:
Received 6 September 2012
Revised 24 September 2012
Accepted 26 September 2012
Available online 3 October 2012

Keywords:
Enaminones
Benzalacetones
1,2-Aryl migration
1,3-Dipolar reaction
Benzylidene acetones

ABSTRACT

Reaction of benzalacetones and dibenzalacetones with benzyl azide promoted by $BF_3{\cdot}OEt_2$ afforded *Z* and *E* densely substituted acyclic α-aryl enaminones in 21–95% yield. For benzalacetones major *Z*-isomers were obtained, while *E*-isomers were the tendency for dibenzalacetones. The synthesis involves domino 1,3-dipolar cycloaddition and 1,2-aryl migration, and is the first metal free practical alternative to the preparation of acyclic α-aryl enaminones from commercial available or easily prepared starting materials.

Introduction

The synthesis of enaminones is a theme of ongoing interest[1] because this class of compound is a versatile intermediate in organic synthesis[2] as well as due to their biological activity.[3] Among the available methods for enaminone's synthesis, the method which employ the reaction of amines with 1,3-dicarbonyl compounds has been intensively investigated.[1,4] However, in the case of unsymmetrical 1,3-diketones, mixtures of regioisomeric enaminones are formed due to the no discrimination of the two electrophilic ketone moieties. To circumvent this limitation there is no satisfactory solution yet.

Recently, Aubé and co-workers described their study concerning the acid promoted (TMSOTf, $BF_3{\cdot}OEt_2$, and TFA) reaction of alkyl azides with cyclic enones, wherein enaminones were obtained, but only one example of enaminone from an acyclic enone was reported, Figure 1.[5] In this context, Johnston and co-workers described the TfOH-promoted addition of electron-rich azides with methyl vinyl ketone affording aziridines.[6] Complementarily, Casey et al. showed that cyclic γ,δ-unsaturated β-diketones react with hydrazoic acid in the presence of H_2SO_4 as solvent, affording cyclic enaminones in good yields.[7] This late reaction is an extension of the reaction of HN_3 and a chalcone activated by electron-withdrawing substituent, which yielded acyclic *N*-aryl enaminone, as described many years ago by Donald and Marks. This late protocol

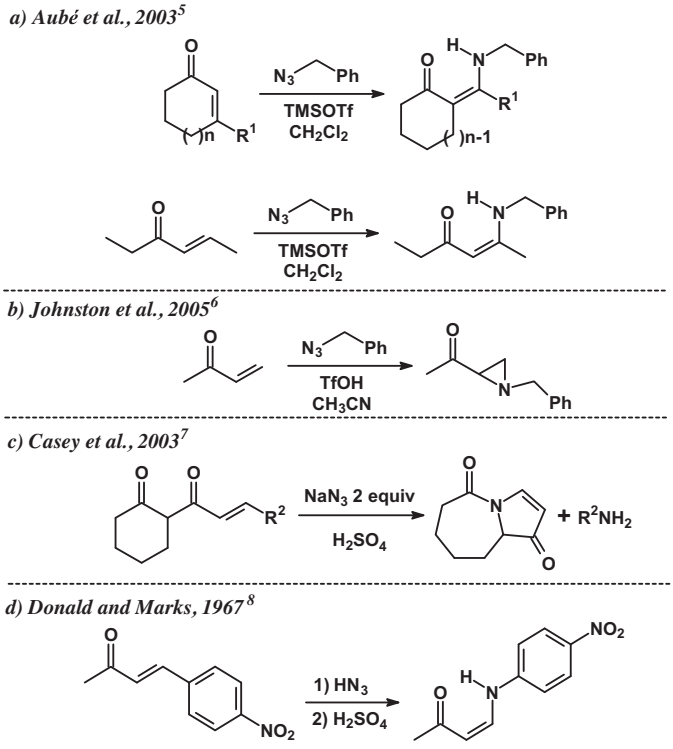
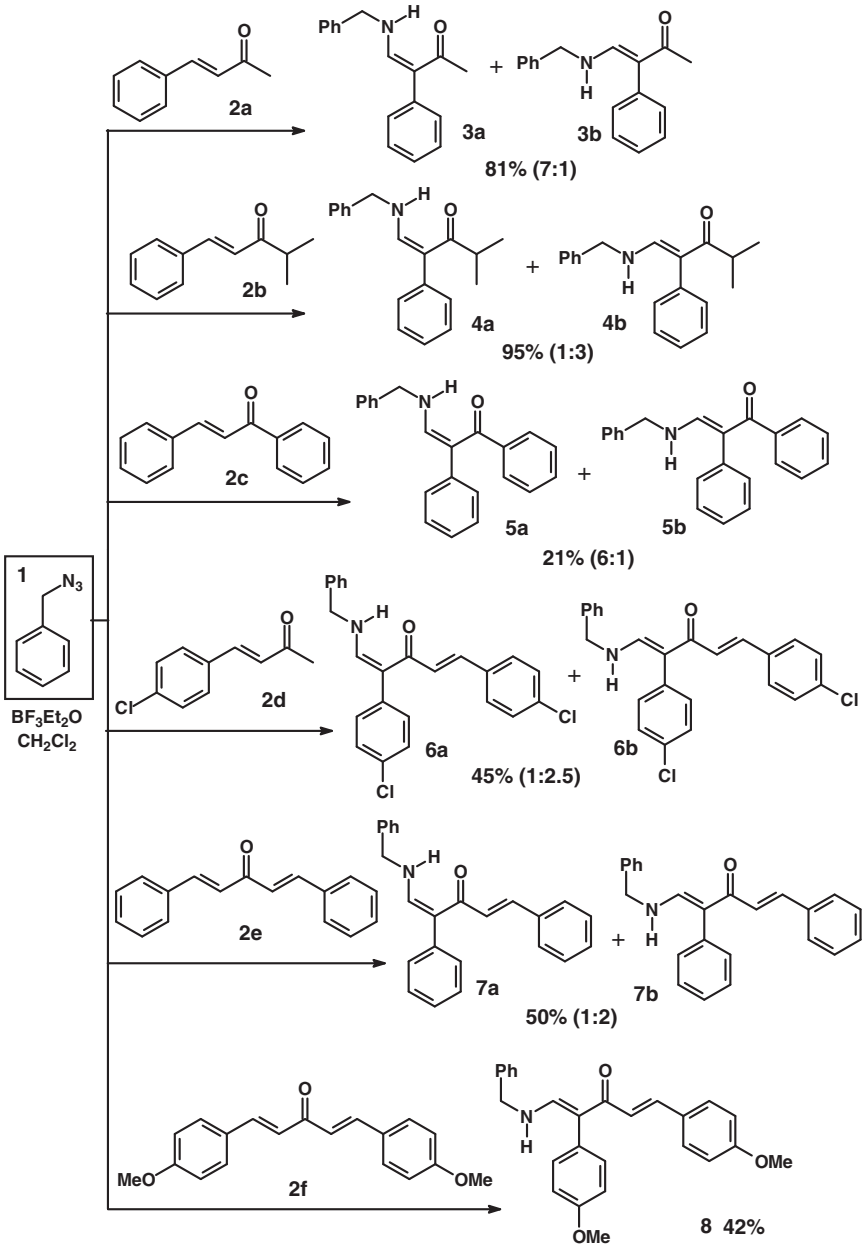


Figure 1. Previously described azide-enone route to enaminones.

* Corresponding author.
E-mail address: silviodc@ufba.br (S. Cunha).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.09.125



Scheme 1. Synthesis of α-aryl enaminones.

represents the first and unique description of synthesis of enaminone employing a β-aryl enone as precursor.[8]

Despite the great contribution of the studies described in Figure 1, there is no report of acyclic α-aryl enaminone synthesis by the 'azide-enone' route. Besides, new one-pot routes to α-aryl enaminones is desirable because these enaminones are advanced intermediates in the synthesis of alkaloids,[2q] and antibacterial compounds.[3a]

Our continued fascination for the chemistry of enaminones[9] prompted us to rationalize that the introduction of an aryl group at the beta position of the enone should circumvents the limitation of the 'azide-enone' route to enaminones, due to the potential aryl neighboring-group participation via a phenonium ion that, in specific cases, should results in its 1,2-migration,[1d,10] as in the condition described by Aubé and co-workers in the synthesis of densely substituted acyclic enaminones.[5] Thus, we disclosure herein our results concerning the one-pot synthesis of α-aryl enaminones through the reactions of acyclic β-aryl enones with benzyl azide, with emphasis on synthetic and mechanistic implications.

Results and discussion

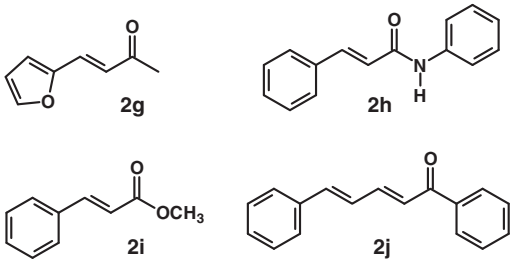
To explore a direct one-pot route towards acyclic α-aryl enaminones from β-aryl enones and benzyl azide **1**, this late was reacted with **2a** in CH_2Cl_2, Scheme 1. After experimentation, the best proportion of enone and benzyl azide was 1:2, using 2 and 3 equiv of $BF_3{\cdot}Et_2O$ (H_2SO_4 and TFA were inefficient).[5] ^1H NMR analyses of the crude reaction mixture after usual workup revealed that the isomeric enaminones **3a–3b** were obtained in good yield. Chromatographic purification afforded enhanced samples of each isomer.

Contrary to the previous description of acyclic enone reaction with benzyl azide,[5] no 1,2-*H* migration was observed in the reaction of **2a**. Instead of this, all obtained compounds were α-aryl

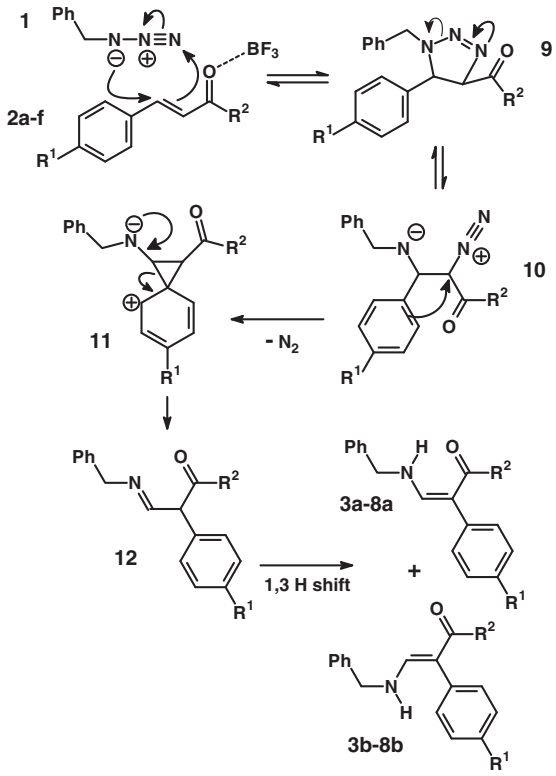
enaminones, which were formed from the planned 1,2-aryl migration, and the spectral ^{1}H NMR analyses permitted the structural assignments of each one as well as the aryl shift confirmation. For instance, for isolated *Z* isomer **3a** the typical deshielding enaminone N–H (δ 10.60 ppm) was observed due to the hydrogen bonding with the carbonyl group, corroborating the assigned configuration, while the N–H signal of *E* isomer **3b** appears at δ 7.45 ppm. These data are in accordance with NMR description of reported β-aryl enone isomers whose structures were elucidated by X-ray also.[11] The phenyl regiochemistry could be easily identified due to the disappearing of original olefinic C–H$_\alpha$ of the enone moiety and, moreover, the presence of C–H$_\beta$ ^3J coupling with the N–H at beta position. No such coupling would be observed for the opposite phenyl regiochemistry. Continuing in this line of reasoning and additional comparison of full spectral data of obtained enaminones **3–8** to analogous *Z* (and *E*) α-aryl (and β-aryl) enaminones described in the literature[11] supported the structural determination of all enaminones here synthesized.

The protocol was applied to enones **2b–c** and, as occurred to **2a**, the major *Z* isomer was formed. However, when *p*-chlorobenzalacetone **2d** was submitted to the same reaction condition, the enaminone moiety could be assigned based on NMR spectra, but no methyl group was detected in the isolated product. Instead of this, additional four aromatic hydrogen and four aromatic carbon signal were observed, and also a vinyl moiety with *trans* stereochemistry (^3J 15.6 Hz), which suggests methyl group transformation. In this way, the structures of isomeric enaminones **6a–b** were deduced. Formation of these enaminones from *p*-chlorobenzalacetone **2d**, where the methyl moiety was functionalized, is in contrast with the behavior of the closed related benzalacetones **2a–c**, Scheme 1. Apparently, the presence of the electron-withdrawing chlorine at the aromatic ring in **2d** induces a retro Claisen–Schmidt reaction promoted by the Lewis acid, forming *p*-chlorobenzaldeyde and acetone, which now react to afford the corresponding dibenzalacetone, and this late suffer the domino reactions with benzyl azide to yield enaminones **6a–b**. To support the hypothesis that dibenzalacetones are reactive substrates for the synthesis of α-aryl enaminones via the azide-enone route, and to corroborate the structure of enaminones **6a–b**, compounds **2e–f** were treated with benzyl azide and enaminones **7a,b–8** could be isolated. For tested dibenzalacetones **2e–f** the observed stereochemical preference was to the *E* enaminone, being this isomer the major (**6b**, **7b**) or the sole (**8**) one detected in the reaction mixture.

To gain further insight into the scope and limitation of the developed protocol, extension of the reaction condition to compounds depicted in Scheme 2 were investigated. These substrates were selected as representative structural variations involving the carbonyl (amide **2h** and ester **2i**) and the olefin (heterocyclic **2g** and α,β,γ,δ-unsaturated **2j**) moieties. However, these substrates did not afford the corresponding enaminones, being recovered even after prolonged reaction time for **2g** and **2i**, or a complex mixture was formed for **2h** and **2j** (analyzed by spectroscopic and chromatographic techniques). In this way, the formation of α-aryl



Scheme 2. Compounds which do not afforded enaminones.



Scheme 3. Proposed mechanism to the formation of enaminones **3**–**8**.

enaminones is limited to simple α,β-unsaturated ketones as **2a–d**, being tolerated variation at the carbonyl moiety as in **2e–f**.

Mechanistically, formation of enaminones can be rationalized as a domino process initiated by 1,3-dipolar cycloaddition of the benzyl azide **1** and the olefinic moiety of the enones **2a–f**, Scheme 3, as pointed out by Aubé and co-workers.[5] In the sequence, the opening of the unstable dihydro triazole ring **9** occurs, and the nitrogen extrusion is assisted by the aromatic ring in **10**, and then the rearomatization step of phenonium ion **11** affords the 1,2-aryl migration product **12**, which thus yield enaminones **3–8** after 1,3*H* shift.

In conclusion, this study shows that the rational combination of 'BF_3·Et_2O-induced phenyl migration'[1d] and 'BF_3·Et_2O-azide-enone'5 route applied to acyclic β-aryl enones and benzyl azide can be a practical synthetic route to densely substituted acyclic α-aryl enaminones, being an alternative methodology to access this synthetically important class of compound from commercial available or easily prepared starting materials.

Acknowledgments

The authors gratefully acknowledge the financial support of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB). We also thank CNPq for fellowship to A.T.G., and a research fellowship to S.C., and Professor Mauricio Victor for the comments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.125.

References and notes

1. (a) Rafiee, E.; Joshaghani, M.; Eavani, S.; Rashidzadeh, S. *Green Chem.* **2008**, *10*, 982–989; (b) Zhang, Y.; Li, D.; Zhou, G.; Xia, C.; Guo, W. *Heterocycles* **2008**, *75*,

1123–1131; (c) Palimar, S. S.; More, V. S.; Srinivasan, K. V. *Synth. Commun.* **2008**, *38*, 1456–1469; (d) Gioiello, A.; Venturoni, F.; Natalini, B.; Pellicciari, R. *J. Org. Chem.* **2009**, *74*, 3520–3523; (e) Xu, X.; Du, P.; Cheng, D.; Wang, H.; Li, X. *Chem. Commun.* **2012**, 1811–1813; (f) Neupane, P.; Li, X.; Jung, J. H.; Lee, Y. R.; Kim, S. H. *Tetrahedron* **2012**, *68*, 2496–2508; (g) Liu, P.; Shan, G.; Chen, S.; Rao, Y. *Tetrahedron Lett.* **2012**, *53*, 936–939; (h) Indulkar, U. U.; Kale, S. R.; Gawande, M. B.; Jayaram, R. V. *Tetrahedron Lett.* **2012**, *53*, 3857–3860.

2. For reviews see: (a) Lue, P.; Greenhill, J. V. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1997; Vol. 67, pp 207–343; (b) Kuckländer, V. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1994; pp 525–639. Part 1; (c) Elliott, M. C.; Wood, J. L.; Wordingham, S. V. *Trends Heterocycl. Chem.* **2005**, *10*, 73–95; (d) Ferraz, H. M.; Gonçalo, E. R. S. *Quim. Nova* **2007**, *30*, 957–964; (e) Cheng, Y.; Huang, Z. T.; Wang, M.-X. *Curr. Org. Chem.* **2004**, *8*, 325–351; (f) Ferraz, H. M. C.; Pereira, F. L. C. *Quim. Nova* **2004**, *27*, 89–95; (g) Negri, G.; Kascheres, C.; Kascheres, A. J. J. *Heterocycl. Chem.* **2004**(41), 461–491; (h) Kascheres, C. *J. Braz. Chem. Soc.* **2003**(14), 945; (i) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463–8480; (j) Kostyuk, A. N.; Volochnyuk, D. M.; Sibgatulin, D. A. *Synthesis* **2008**, 161–184; (k) Michael, J. P.; Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979–988; For representative applications see: (l) Braibante, M. E. F.; Braibante, H. T. S.; Uliana, M. P.; Costa, C. C.; Spenazzatto, M. *J. Braz. Chem. Soc.* **2008**, *19*, 909–913; (m) Flores, A. F. C.; Flores, D. C.; Oliveira, G.; Pizzuti, L.; Silva, R. M. S.; Martins, M. A. P.; Bonacorso, H. G. *J. Braz. Chem. Soc.* **2008**, *19*, 183–193; (n) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2626–2632; (o) Santarem, M.; Vanucci-Bacqué, C.; Lhommet, G. *J. Org. Chem.* **2008**, *73*, 6466–6469; (p) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836–5838; (q) Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637–6641.

3. (a) Xiao, Z.-P.; Xue, J.-Y.; Tan, S.-H.; Li, H.-Q.; Zhu, H.-L. *Bioorg. Med. Chem.* **2007**, *15*, 4212–4219; (b) Xiao, Z.-P.; Fang, R.-Q.; Li, H.-Q.; Xue, J.-Y.; Zheng, Y.; Zhu, H.-L. *Eur. J. Med. Chem.* **2008**, *43*, 1828–1836; (c) Foster, J. E.; Nicholson, J. M.; Butcher, R.; Stables, J. P.; Edafiogho, I. O.; Goodwin, A. M.; Henson, M. C.; Smith, C. A.; Scott, K. R. *Bioorg. Med. Chem.* **1999**, *7*, 2415–2425; (d) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Stables, J. P.; Powell, C. B.; Scott, K. R. *Curr. Med. Chem.* **2000**, *7*, 417–436.

4. (a) Andrade, C. K. Z.; Fátima, A.; Barreto, A. S.; Silva, W. A. *Arkivoc* **2008**, *12*, 226–232; (b) Chem, X.; She, J.; Shang, Z.; Wu, J.; Wu, H.; Zhang, P. *Synthesis* **2008**, 3478–3486; (c) Sridharam, V.; Avendaño, C.; Menéndez, J. C. *Synllet* **2007**, 881–884; (d) Braibante, M. E. F.; Braibante, H. S.; Missio, L.; Andricopulo, A. *Synthesis* **1994**, 898–900; (e) Braibante, M. E. F.; Braibante, H. S.; Salvatore, S. J. S. A. *Quim. Nova* **1990**, *13*, 67–68; (f) Braibante, H. S.; Braibante, M. E. F.; Rosso, G. B.; Oriques, D. A. *J. Braz. Chem. Soc.* **2003**, *14*, 994–997; (g) Braibante, M. E. F.; Braibante, H. S.; Morel, A. F.; Costa, C. C.; Lima, M. G. *J. Braz. Chem. Soc.* **2006**, *17*, 184–188.

5. Reddy, D. S.; Judd, W. R.; Aubé, J. *Org. Lett.* **2003**, *5*, 3899–3902.

6. Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354–1355.

7. Casey, M.; Donnelly, J. A.; Ryan, J. C.; Ushioda, S. *Arkivoc* **2003**, *7*, 310–327.

8. Donald, A. S. R.; Marks, R. E. *J. Chem. Soc. C* **1967**, 1188–1189.

9. (a) Cunha, S.; Damasceno, F.; Ferrari, J. *Tetrahedron Lett.* **2007**, *48*, 5795–5798; (b) Cunha, S.; Bastos, R. M.; Silva, P. O.; Costa, G. A. N.; Vencato, I.; Lariucci, C.; Napolitano, H. B.; Oliveira, C. M. A.; Kato, L.; Silva, C. C.; Menezes, D.; Vannier-Santos, M. A. *Monatsh. Chem.* **2007**, *138*, 111–119; (c) Cunha, S.; Silva, V. C.; Napolitano, H. B.; Lariucci, C.; Vencato, I. *J. Braz. Chem. Soc.* **2003**, *14*, 107–112; (d) Cunha, S.; Rodovalho, W.; Azevedo, N.; Mendonça, M. O.; Lariucci, C.; Vencato, I. *J. Braz. Chem. Soc.* **2002**, *13*, 629–634; (e) Cunha, S.; Kascheres, A. *J. Braz. Chem. Soc.* **2001**, *12*, 481–484.

10. Anslyn, E. V.; Dougertty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Salsalito, 2006. pp 659–661.

11. Xiao, F.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5789–5791.