Tetrahedron Letters 54 (2013) 2641–2644

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Thermally-induced ring contraction as a novel and straightforward route for the synthesis of 2-furyl acetonitrile derivatives

Arash Mouradzadegun *, Fatemeh Abadast

Department of Chemistry, Faculty of Science, Shahid Chamran University, Ahvaz, Iran

ARTICLE INFO

Article history:
Received 29 January 2013
Revised 25 February 2013
Accepted 7 March 2013
Available online 15 March 2013

Keywords:
2-Furyl acetonitrile
Pyrylium salts
Nucleophilic reaction
Ring contraction

ABSTRACT

A new, efficient, and simple process has been established for the synthesis of (3,5-diaryl-2-furyl)(aryl)acetonitriles by the reaction of various 2,4,6-triarylpyrylium perchlorates with sodium cyanide.

Furan derivatives occur widely as essential structural units in a variety of natural products.[1] They are also present in commercially important products such as agrochemical bioregulators, dyes and photosensitizers, essential oils, and flavoring and fragrance compounds.[2] Moreover, the utility of this moiety as a building block and intermediate[3] in synthesis has received considerable attention,[4] in addition to their wide range of biological activities.[5] Among them, 2-furyl acetonitrile derivatives have found use as key intermediates toward the fatty acid derivatives, plakorsins A and B,[6] isolated from the marine sponge, *Plakortis simplex*,[7] which demonstrate useful cytotoxic activities against various cancer cell lines.

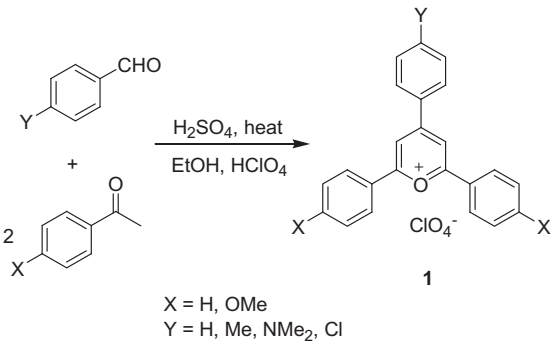
Due to the aforementioned chemical and pharmacological significance, the development of direct and convenient methods to generate furan derivatives from simple, readily available starting materials has attracted considerable interest.[8] Although a variety of strategies have been reported in this area,[9] most methods suffer from one or more drawbacks such as long reaction times, multiple steps, the use of expensive transition metal catalysts, and harsh reaction conditions. Therefore, further improvements are required for the synthesis of these molecules.

Pyrylium salts represent, more so than other heterocyclic systems, a nodal point for many synthetic routes as they can function as intermediates for a very wide variety of syntheses.[10] They owe their key role to their reactivity toward nucleophiles.

Despite many advances in the chemistry of pyrylium salts, there have been no reports on the use of these salts as substrates for the synthesis of 2-furyl acetonitrile derivatives. In continuation of our studies on the development of practical and eco-friendly procedures for various important reactions and transformations,[11] herein, we report for the first time, the applicability of thermally-induced ring contractions for the convenient synthesis of 2-furyl acetonitrile derivatives from the readily accessible corresponding pyrylium salts.

2,4,6-triarylpyrylium perchlorates were easily synthesized from the corresponding aldehydes and ketones by the previously described method[10,12] (Scheme 1).

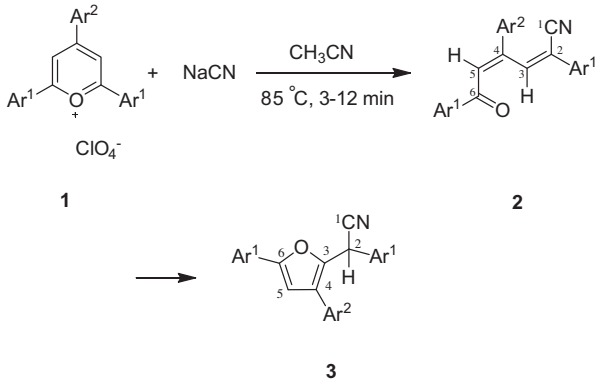
To develop suitable reaction conditions, 2,4,6-triphenylpyrylium perchlorate was chosen as a model compound and parameters including solvent, temperature, and molar ratio of the reagent and substrate were examined in detail.



Scheme 1. Synthesis of 2,4,6-triarylpyrylium perchlorates **1**.

* Corresponding author. Tel.: +98 611 3331042; fax: +98 611 3337009.
E-mail address: arash_m@scu.ac.ir (A. Mouradzadegun).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.03.033



Scheme 2. Synthesis of (3,5-diaryl-2-furyl)(aryl)acetonitriles **3** via the reaction of various triarylpyrylium perchlorates **1** with NaCN.

Among the solvents investigated which included ethanol, tetrahydrofuran, dichloromethane, and acetonitrile, the best result in terms of yield was obtained with acetonitrile.

The reaction was also evaluated at different temperatures. At room temperature, the reaction of 2,4,6-triphenylpyrylium perchlorate **1** with sodium cyanide gave the corresponding cyanodienone **2** as the sole product. There was no evidence of the transformation into 2-furyl acetonitrile **3** according to TLC analysis. The facile nature of this reaction is testament to the high chemical potential of the pyrylium nucleus which, despite its aromaticity, is easily opened under such mild conditions. Surprisingly, raising the temperature led to the formation of the cyanodienone **2** along with a small amount of product **3**. The formation of **3**, which might occur through a cyanodienone intermediate, is of considerable interest since it is the first example of ring contraction involving a carbon nucleophile instead of the customarily applied nitrogen or oxygen nucleophiles. The highest yield of product **3** was obtained at reflux temperature. Hence, the reaction was run at reflux temperature in all subsequent cases (Scheme 2).

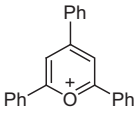
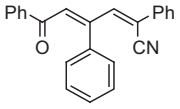
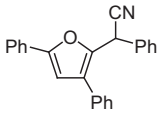
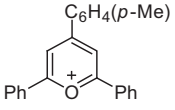
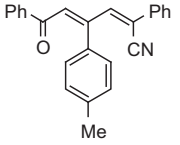
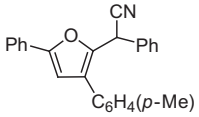
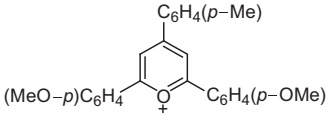
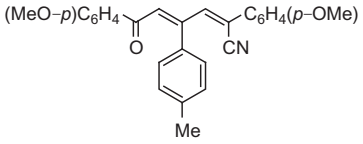
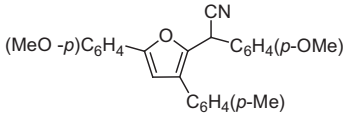
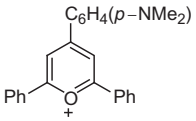
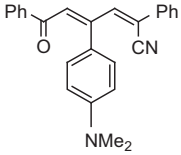
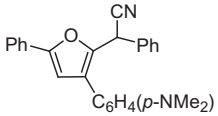
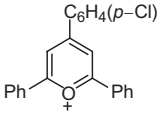
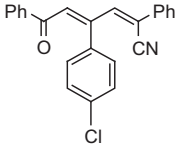
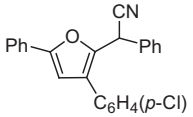
Table 1
Optimization of the reagent/substrate ratio

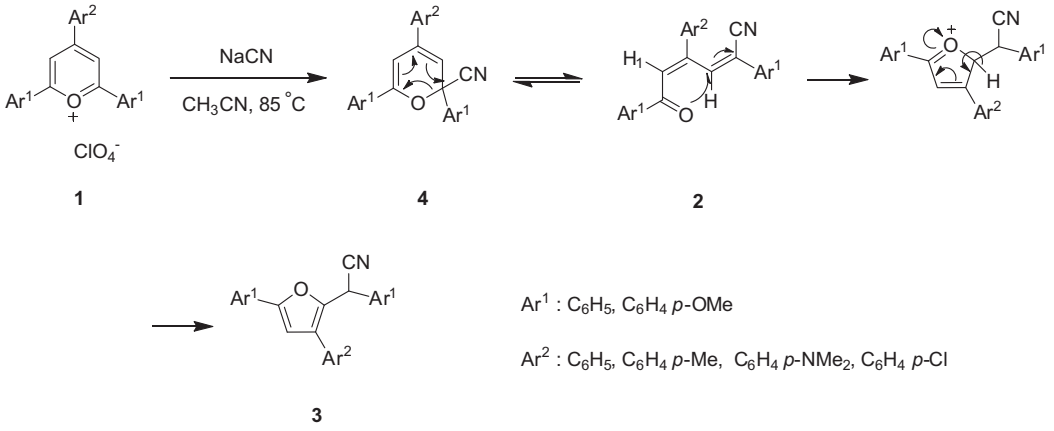
Entry	Reagent/substrate	Time (min)	Yield of **3** (%)
1	1	20	60
2	1.5	15	60
3	2	7	60
4	2.5	5	53

Next, the reaction of model compound **1** (1 mmol) with varying amounts of sodium cyanide was investigated. As shown in Table 1, the target product was favored by increasing the reagent/substrate ratio as indicated by the significant decrease in the reaction time. Bearing in mind that the reaction proceeds through an addition/ring-opening mechanism, the increase in reagent concentration favors the first reaction step and, on the whole, product formation. The decrease in the yield (53%) employing a ratio of 2.5 (entry 4) can probably be explained due to the generation of by-products. The best yield (60%) and the shortest reaction time (7 min) were obtained using a ratio of reagent/substrate = 2 (entry 3).

The scope of this protocol was then investigated under the optimized reaction conditions.[13] Substituted 2,4,6-triarylpyrylium perchlorates (1 mmol) were subjected to the reaction with NaCN (2 mmol) in acetonitrile (10 ml) under reflux conditions (Table 2). Substrates with electron-donating groups led to decreased reaction rates (entries A–D). This can be rationalized by considering the fact that these groups decrease the positive charge at the α-position of

Table 2
The conversion of various triarylpyrylium salts into the corresponding (3,5-diaryl-2-furyl)(aryl)acetonitriles at 85 °C

Entry	Substrate	Intermediate (**2**)	Product (**3**)	Time (min)	Yield (%)
A				7	60
B				9	61
C				10	71
D				12	66
E				3	60



Scheme 3. A plausible mechanism for the formation of furan derivatives **3**.

the heterocyclic ring. The presence of stronger electron-donating groups led to even longer reaction times. In contrast, an electron-withdrawing group (entry E) accelerated the reaction.

The structures of compounds **2** and **3** were established unambiguously from physical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) data.

On the basis of the results obtained above, a potential reaction mechanism involves the formation of α-cyanopyran **4** in the first step, which is readily converted into cyanodienone **2** through a tautomeric process (Scheme 3). It is postulated that this non-aromatic product is the common intermediate which in turn undergoes ring-closure and hydrogen abstraction to give 2-furyl acetonitrile derivatives **3**. This assumption was proved by isolating the cyanodienone intermediates and subjecting them to direct conversion into the 2-furyl acetonitriles on heating.

In summary, we have described a new, direct, and reliable thermally-induced ring contraction pathway for the synthesis of several 2-furyl acetonitrile derivatives. To the best of our knowledge, this is the first example of the formation of 2-furyl acetonitrile products starting from pyrylium salts. We anticipate that this new and viable route should be useful to both research and pharmaceutical development endeavors.

Acknowledgment

This work was supported by the Research Council of the University of Shahid Chamran.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.033.

References and notes

1. (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795; (b) Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, 2002; Vol. 14, (c)Eicher, T., Hauptmann, S., Eds.The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications; Wiley-VCH: Weinheim, 2003; (d) Hou, X. L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2003**, *15*, 167; (e) Rodriguez, A.; Moran, W. J. *Tetrahedron Lett.* **2011**, *52*, 2605.
2. (a) Blunt, J. W.; Copp, B. R.; Munro, M. H.; Northcote, G. P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *17*, 235; (b) Zanatta, N.; Alves, S. H.; Coelho, H. S.; Borchhardt, D. M.; Machado, P.; Flores, K. M.; da Silva, F. M.; Spader, T. B.; Santurio, J. M.; Bonacorso, H. G.; Martins, M. A. P. *Bioorg. Med. Chem.* **2007**, *15*, 1947.
3. (a) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995; p 231; (b) Lavieri, R.; Scott, S. A.; Lewis, J. A.; Selvy, P. E.; Armstrong, M. D.; Alex Brown, H.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2240; (c) Bateman, T. D.; Joshi, A. L.; Moona, K.; Galitovskaya, E. N.; Upreti, M.; Chambers, T. C.; McIntosh, M. C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6898; (d) Cushman, M.; Sambaiah, T.; Jin, G.; Llarionov, B.; Fischer, M.; Bacher, A. *J. Org. Chem.* **2004**, *69*, 601; (e) Kim, S.; Kang, D.; Shin, S.; Lee, P. H. *Tetrahedron Lett.* **2010**, *51*, 1899.
4. (a) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558; (b) Ouairy, C.; Michel, P.; Delpech, B.; Crich, D.; Marazano, C. *J. Org. Chem.* **2010**, *75*, 4311.
5. (a) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 4, p 657; (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1955**, *1998*, 54; (c) Barancelli, D. A.; Mantovani, A. C.; Jesse, C.; Nogueira, C. W.; Zeni, G. *J. Nat. Prod.* **2009**, *72*, 857; (d) Cho, C. H.; Shi, F.; Jung, D. I.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *ACS Comb. Sci.* **2012**, *14*, 403.
6. (a) Hayes, S. J.; Knight, D. W.; Smith, A. W. T.; O'Halloran, M. J. *Tetrahedron Lett.* **2010**, *51*, 717; (b) Al-Busafi, S.; Doncaster, J. R.; Drew, M. G. B.; Regan, A. C.; Whitehead, R. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 476.
7. Shen, Y. C.; Prakash, C. V.; Kuo, Y. H. *J. Nat. Prod.* **2001**, *64*, 324.
8. (a) Lee, C. F.; Yang, L. M.; Hwu, T. Y.; Feng, A. S.; Tseng, J. C.; Luh, T. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992; (b) Graening, T.; Thrun, F. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier Science: Oxford, 2008; Vol. 3, pp 498–561. Chapter 7, and references therein.
9. (a) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277; (b) Mross, G.; Holtz, E.; Langer, P. *J. Org. Chem.* **2006**, *71*, 8045; (c) Xu, B.; Hammond, G. B. *J. Org. Chem.* **2006**, *71*, 3518; (d) Fu, Z.; Wang, M.; Ma, Y.; Liu, Q.; Liu, J. *J. Org. Chem.* **2008**, *73*, 7625; (e) Zhao, L. B.; Guan, Z. H.; Han, Y.; Xie, Y. X.; He, S.; Liang, Y. M. *J. Org. Chem.* **2007**, *72*, 10276; (f) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376; (g) Babudri, F.; Cicco, S. R.; Farinola, G. M.; Lopez, L. C.; Naso, F.; Pinto, V. *Chem. Commun.* **2007**, 3756; (h) Blanc, A.; Tenbrink, K.; Weibel, J. M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342.
10. Balaban, A. T.; Dinculescu, A.; Dorofeenko, G. N.; Fischer, G. W.; Koblik, A. V.; Mezheritskii, V. V.; Schroth, W. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1982; Vol. 2,. Suppl. 1.
11. (a) Mouradzadegun, A.; Gheitasvand, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1385; (b) Ganjali, M. R.; Norouzi, P.; Emami, M.; Golmohamadi, M.; Pirelahi, H.; Mouradzadegun, A. *J. Chin. Chem. Soc.* **2006**, *53*, 1209; (c) Ganjali, M. R.; Akbar, V.; Daftari, A.; Norouzi, P.; Pirelahi, H.; Mouradzadegun, A. *J. Chin. Chem. Soc.* **2004**, *51*, 309; (d) Mouradzadegun, A.; Pirelahi, H. *J. Photochem. Photobiol., A: Chem.* **2001**, *138*, 203; (e) Mouradzadegun, A.; Pirelahi, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *165*, 149; (f) Mouradzadegun, A.; Pirelahi, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *157*, 193; (g) Mouradzadegun, A.; Dianat, Sh. *J. Heterocycl. Chem.* **2009**, *46*, 778; (h) Mouradzadegun, A.; Ghasem Hezave, F.; Karimnia, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185*, 84; (i) Mouradzadegun, A.; Abadast, F. *Monatsh. Chem.* **2013**, *144*, 375.
12. Balaban, A. T.; Schroth, W.; Fischer, G. W. Pyrylium Salts In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1969; Vol. 10, p 241. and references therein.
13. *General procedure for the synthesis of* ***3***: The triarylpyrylium perchlorate **1** (1 mmol) was dissolved in MeCN (10 ml), NaCN (2 mmol) was added and mixture refluxed for 3–12 min. After completion of the reaction, the solvent was evaporated under vacuum and the residue was adsorbed on silica, transferred to a silica column and eluted with a 20:80 mixture of Et_2O:*n*-hexane. The obtained product was recrystallized from EtOH. *(2Z,4E)-6-Oxo-2,4,6-triphenyl-2,4-hexadienenitrile (**2A**).* Yield 78%; yellow crystals, mp 103–105 °C (from EtOH); IR (neat): ν 2218 (CN), 1645 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 1H, H-1), 7.45–8.05 (m, 15H, Ar-H), 8.4 (s, 1H, H-2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.9 (C-2), 119.6 (C-1), 126.2 (C-5), 126.9,

128.8, 129.1, 129.2, 129.4, 129.5, 130.3, 130.6, 133.6 (ArC), 134.1, 138.8, 139.4 (ArC_q), 141.8 (C-3), 151.9 (C-4), 190.6 (C-6) ppm. *(3,5-Diphenyl-2-furyl)(phenyl)acetonitrile (**3A**).* Yield 60%; white crystals, mp 85 °C (from EtOH); $[M^+] = 335$; IR (neat): ν 2245 (CN) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.5 (s, 1H, H-1), 6.8 (s, 1H, H-2), 7.3–7.7 (m, 15H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.4 (C-2), 107.4 (C-5), 117.3 (C-1), 124.4 (ArC), 127.3 (C-4), 127.8–129.6 (ArC), 130.2, 132.5, 133.9 (ArC_q), 141.6 (C-3), 154.8 (C-6) ppm.