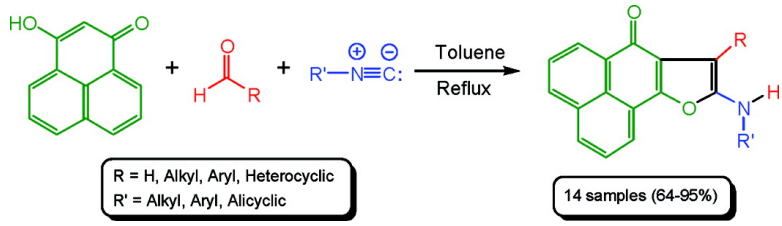
JOURNAL OF combinatorial CHEMISTRY

Article

Simple Synthesis of 7*H*-Phenaleno[1,2-*b*]furan-7-one Derivatives by One-Pot, Three-Component Reactions

Mohammad Bagher Teimouri, and Farideh Mansouri

J. Comb. Chem., **2008**, 10 (4), 507-510• DOI: 10.1021/cc8000103 • Publication Date (Web): 14 June 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Article

Simple Synthesis of 7*H*-Phenaleno[1,2-*b*]furan-7-one Derivatives by One-Pot, Three-Component Reactions

Mohammad Bagher Teimouri*,† and Farideh Mansouri‡

Petrochemical Department, Iran Polymer and Petrochemical Institute, P.O. Box 14965-115, Tehran, Iran, and Faculty of Chemistry, Firouzabad Branch, Islamic Azad University, Firouzabad, Iran

Received January 21, 2008

The reaction of alkyl isocyanides with various aldehydes and 3-hydroxy-1*H*-phenalene-1-one is described. The protocol offers facile and efficient synthesis of biologically interesting 9-(alkyl or arylamino)-7*H*-phenaleno[1,2-*b*]furan-7-one derivatives from readily available starting materials in high yields.

Introduction

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity.[1] One of the ways to fulfill these goals is the development and use of multicomponent reactions which consist of several simultaneous bond-forming reactions and allow the high efficient synthesis of complex molecules starting from simple substrates in a one-pot manner.[2] Multicomponent reactions (MCRs), which can produce a diversity of compounds, provide one of the most efficient methods for the combinatorial synthesis of structurally diverse compounds.[3] Multicomponent reactions can also lead to an increase in molecular complexity by combining a series of reactions in one synthetic operation.[4]

Furophenalenone derivatives are well-known as structural components in natural products, some of which exhibit useful biological activity. For example, atrovenetin **l**, a fungal metabolite of *Penicillium atrouenetum*, belongs to the class of naturally occurring furophenalenones.[5] Atrovenetin is described as an antioxidant[6] and as a cytostatic agent having antineoplastic activity (see Scheme 1).[7]

Although isocyanide-based multicomponent reaction has been applied to the synthesis of various fused furans,[8] to our knowledge, this synthetic strategy has not been applied to the synthesis of substituted furophenalenone. There are only three reports[9–11] on cycloaddition entries into the fused 7*H*-phenaleno[1,2-*b*]furan-7-one ring system involving ring synthesis by formation of two bonds from [3 + 2] atom fragments ([CCO + CC]). All these oxidative cycloaddition reactions employ a two-component condensation between a 3-hydroxy-1*H*-phenalene-1-one derivative and a conjugated alkene or alkyne. The each of is catalyzed in two ways.[9–11]

As early as 1998, Lee and co-workers reported the ceric ammonium nitrate (CAN)-mediated cycloaddition reaction of 3-hydroxy-1*H*-phenalene-1-one with phenylacetylene leading to phenylfurophenalenone in 50% yield.[9] Later, they replaced phenylacetylene with conjugated olefins which led to the corresponding dihydrofurophenalenones in moderate yields.[10] In a second approach, rhodium-catalyzed cycloaddition reactions of 2-diazo-1*H*-phenalene-1,3(2*H*)-dione with allyl halides leads to dihydrofurophenalenones with an *exo*-olefin.[11] Subsequently, treatment of these products with DBU in benzene afforded the corresponding furophenalenone derivatives. To date, we know of no published report concerning the synthesis of furophenalenone ring systems which proceed via the formation of three new bonds by a [CCO + C + C] furannulation strategy.

Continuing our efforts directed toward the straightforward preparation of biologically active heterocycles through isocyanide-based multicomponent reactions[12] herein, we would like to report a facile and efficient procedure for the preparation of 7*H*-phenaleno[1,2-*b*]furan-7-one derivatives **5** through a three-component reaction including 3-hydroxy-1*H*-phenalene-1-one **2**, various aldehydes **3** and alkyl isocyanides **4** in refluxing toluene. The reaction can be represented as in Table 1.

Results and Discussion

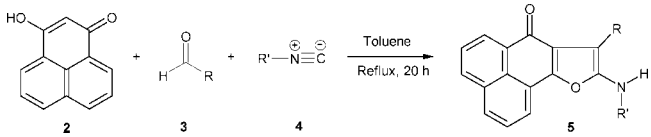
The one-pot, three-component condensation reactions of 3-hydroxy-1*H*-phenalene-1-one **2** with various aldehydes **3** in the presence of alkyl isocyanides **4** proceeded rapidly in refluxing toluene and were complete after 20 h to afford 9-(alkyl or arylamino)-7*H*-phenaleno[1,2-*b*]furan-7-ones **5**, in good yields. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of fused furophenalenone **5**. All the products were characterized by FT-IR, ^{1}H and ^{13}C NMR spectra, and elemental analysis.

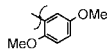
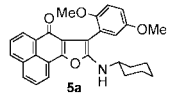
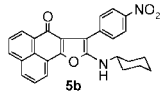
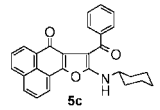
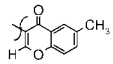
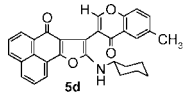
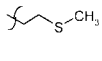
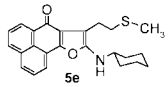
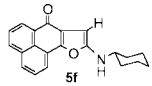
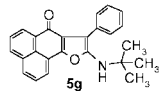
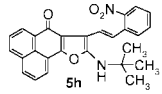
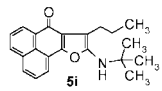
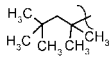
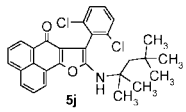
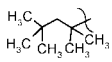
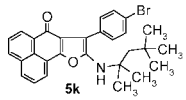
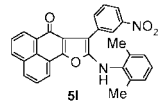
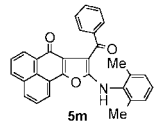
The elucidation of the structure of **5** using ^{1}H and ^{13}C NMR spectroscopic data is discussed with **5a** as an example.

* To whom correspondence should be addressed. E-mail: m.teimouri@ippi.ac.ir. Fax: +98-21-44580023.
† Iran Polymer and Petrochemical Institute.
‡ Islamic Azad University.

10.1021/cc8000103 CCC: $40.75
Published on Web 06/14/2008

Table 1. Synthesis of 7*H*-Phenaleno[1,2-*b*]furan-7-one Derivatives



Entry	R	R'	Product	Yield (%)[a]
1			 **5a**	72
2			 **5b**	93
3			 **5c**	95
4			 **5d**	76
5			 **5e**	80
6	H		 **5f**	64
7			 **5g**	88
8			 **5h**	92
9			 **5i**	81
10			 **5j**	78
11			 **5k**	74
12			 **5l**	65
13			 **5m**	94
14			**5n**	67

[a] Refers to purified yield. Compound purity is >95% as determined by NMR.

The ^{1}H NMR spectrum of **5a** consisted of multiplet signals for the cyclohexyl rings (δ_H 1.20−2.15 ppm) and the NH−C*H* resonance (δ_H 3.78) and two sharp singlets for the methoxy groups (δ_H 3.80 and 3.83 ppm). A broad resonance (δ_H 4.30 ppm) was observed for the NH group. The aromatic hydrogens give rise to multiplet signals in the aromatic region of the spectrum.

Scheme 1. Atrovenetin, a Natural Biologically Active Furophenalenone

The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 27 distinct resonances in agreement with the suggested structure. The ^{1}H decoupled ^{13}C NMR spectra of **5b**−**n** are similar to those of **5a** except for the R or R′ groups, which exhibit characteristic signals with appropriate chemical shifts.[13]

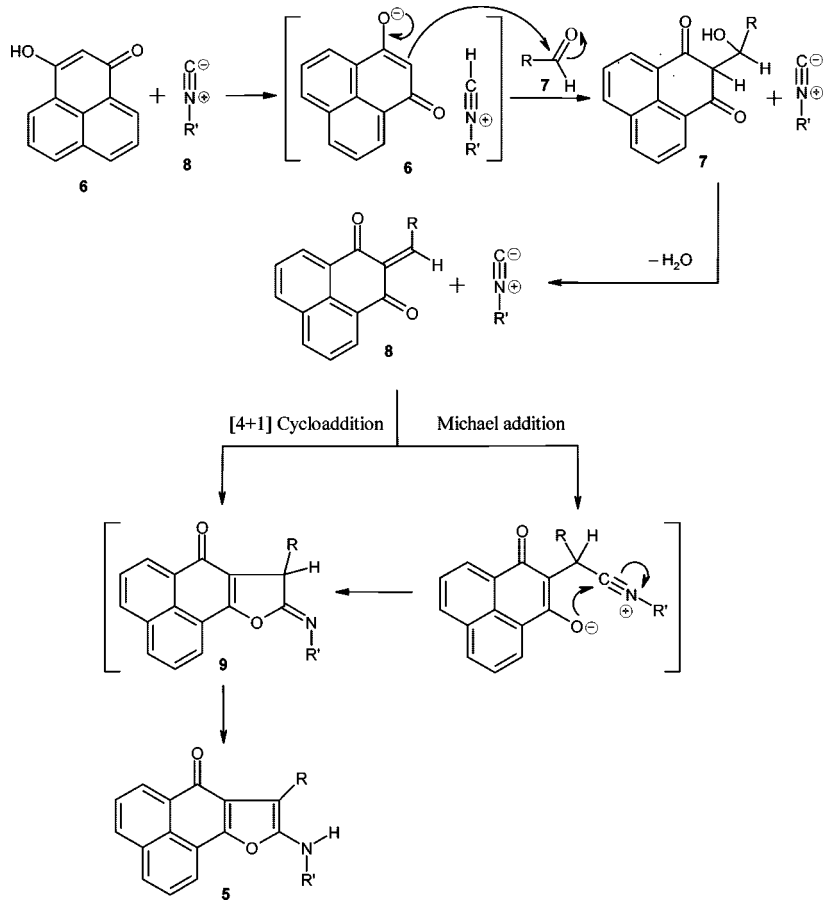
The scope and limitations of the reaction with respect to the aldehyde component was examined, and it was found that aliphatic aldehydes, substituted aromatic aldehydes containing electron-withdrawing groups and electron-donating groups, and α,*β*-unsaturated aldehydes all tolerate the reaction conditions with good yields. Only with 4-(*N,N*-dimethylamino)benzaldehyde did the TLC and ^{1}H NMR spectrum of the reaction mixture clearly indicate a complex mixture of at least five products together with some of the unreacted 3-hydroxy-1*H*-phenalene-1-one and the aldehyde. After purification by silica gel column chromatography with ethyl acetate:*n*-hexane 1:3 as eluent we obtained the corresponding Knoevenagel condensation adduct in 15% yield as a new product. To explore the scope of this reaction with respect to isocyanides, we have examined five alkyl or aryl isocyanides. We have found that the reaction proceeds very efficiently even with hindered alkyl or aryl isocyanides.

Although the mechanism of the reaction between 3-hydroxy-1*H*-phenalene-1-one and aldehyde in the presence of isocyanide has not yet been established experimentally, a possible explanation is proposed in Scheme 2.

The mechanism envisages an initial acid−base reaction of activated CH-acid **2**, 3-hydroxy-1*H*-phenalene-1-one, with isocyanide **4** to give an ion pair complex **6**.[14] The conjugate base of the CH-acid is now sufficiently active for nucleophilic attack to aldehyde **3** to produce intermediate **7**. Intermediate **7** can lose a molecule of water to afford the Knoevenagel condensation adduct **8**. This is presumably followed by [4 + 1] cycloaddition reaction or Michael-type conjugate addition of isocyanide with concomitant cyclization to give iminolactone intermediate **9**. The subsequent isomerization of iminolactone **9** leads to formation of 9-(alkyl or arylamino)-7*H*-phenaleno[1,2-*b*]furan-7-ones **5**. Presumably, the isomerization of **9** to **5** is driven by the stability of the fully conjugated aminofuran heteroaromatic moiety.

In order to confirm the mechanism of the reaction in Scheme 2, we examined the reaction of the 3-hydroxy-1*H*-phenalene-1-one with aldehydes under the same reaction conditions without isocyanide component to produce the Knoevenagel condensation adduct **8**. Our attempts to carry out this reaction with a wide range of aliphatic and aromatic aldehydes, from highly electron-rich such as 4-(*N,N*-dim-

Scheme 2. Possible Mechanism for the Formation of Products **5a**−**n**



ethylamino)benzaldehyde to highly electron-poor such as 4-nitrobenzaldehyde were not successful. For all of the aldehydes apart from 4-nitrobenzaldehyde the TLC of the reaction mixture clearly indicated that the Knoevenagel adduct **8** was not formed, and starting materials (3-hydroxy-1*H*-phenalene-1-one and aldehyde) recovered unchanged. In the case of the reaction of 3-hydroxy-1*H*-phenalene-1-one with 4-nitrobenzaldehyde, after refluxing for 20 h in toluene, the corresponding Knoevenagel adduct **8b** was isolated in 8% yield, but this same reaction in the presence of cyclohexyl isocyanide has afforded 9-(cyclohexylamino)-8-(4-nitrophenyl)-7*H*-phenaleno[1,2-*b*]furan-7-one **5b** (Table 1, Entry 2) in 93% yield. These results have made us to establish a significant catalytic role for isocyanide component in Knoevenagel condensation reaction of 3-hydroxy-1*H*-phenalene-1-one with aldehyde.

Finally, the 2-[(4-nitrophenyl)methylene]-1*H*-phenalene-1,3(2*H*)-dione **8b** as a representative Knoevenagel condensation adduct **8** was synthesized separately by the condensation of 4-nitrobenzaldehyde and 3-hydroxy-1*H*-phenalene-1-one in toluene at refluxed overnight under 10 mol % of HCl catalysis. Then, we examined the reaction of the isolated 2-[(4-nitrophenyl)methylene]-1*H*-phenalene-1,3(2*H*)-dione **8b** with one equivalent amount of cyclohexyl isocyanide in refluxing toluene, and we obtained the product **8b** in 95%.

In conclusion, we have developed a simple, one-pot, three-component procedure for the preparation of 9-(alkyl or arylamino)-7*H*-phenaleno[1,2-*b*]furan-7-one derivatives of potential synthetic and biological interest. The method is simple, starts from readily accessible commercial reagents, and provides biologically interesting furophenalenone derivatives in good yields without any other additive to promote the reaction. Moreover, it is worth noting that two C−C and one C−O bonds were formed with concomitant creation of a fused furophenalenone ring in this one-pot, three-component process.

Acknowledgment. We would like to thank Iran Polymer and Petrochemical Institute (IPPI) research council for the financial support.

Supporting Information Available. Experimental procedures and spectra of the compounds **5a**−**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Trost, B. M. *Science* **1991**, *254*, 1471–1477.
(2) (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmidt, P. *Chem.*−*Eur. J.* **2000**, *6*, 3321–3329. (b) von Wangelin, A. J.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem.*−*Eur. J.* **2003**, *9*, 4286–4294. (c) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499.
(3) (a) Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1–15. (b) Tejedor, D.; González-Cruz, D.; Santos-Expósito, A.; Marrero-Tellado, J. J.; de Armas, P.; García-Tellado, F. *Chem.*−*Eur. J.* **2005**, *11*, 3502–3510.
(4) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144, and references therein.
(5) (a) Neill, K. G.; Raistrick, H. *Biochem. J.* **1957**, *65*, 166–

176. (b) Barton, D. H. R.; deMayo, P.; Morrison, G. A.; Raistrick, H. *Tetrahedron* **1959**, *6*, 48–62. (c) Büchi, G.; Leung, J. C. *J. Org. Chem.* **1986**, *51*, 4813–4818.

(6) Ishikawa, Y.; Morimoto, K.; Iseki, S. *J. Am. Oil Chem. Soc.* **1991**, *68*, 666–668.

(7) Weber, E.; Tseng, B. Y.; Drewe, J.; Cai, S. X. Methods of identifying therapeutically effective antineoplastic agents with cultured cells having intact cell membranes and corresponding products. WO 0045165, 2000.

(8) (a) Nair, V.; Menon, R. S.; Vinod, A. U.; Viji, S. *Tetrahedron Lett.* **2002**, *43*, 2293–2295. (b) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2002**, *43*, 9151–9154. (c) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Monatsh. Chem.* **2004**, *135*, 441–446. (d) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Monatsh. Chem.* **2004**, *135*, 589–593. (e) Shaabani, A.; Teimouri, M. B.; Samadi, S.; Soleimani, K. *Synth. Commun.* **2005**, *35*, 535–541. (f) Teimouri, M. B.; Bazhrang, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3697–3701. (g) Teimouri, M. B.; Khavasi, H. R. *Tetrahedron* **2007**, *63*, 10269–10275.

(9) Lee, Y. R.; Byun, M. W.; Kim, B. S. *Bull. Korean Chem. Soc.* **1998**, *19*, 1080–1083.

(10) Lee, Y. R.; Kim, B. S.; Kim, D. H. *Tetrahedron* **2000**, *56*, 8845–8853.

(11) Lee, Y. R.; Suk, J. Y. *Tetrahedron* **2002**, *58*, 2359–2367.

(12) (a) Teimouri, M. B. *Tetrahedron* **2006**, *62*, 10849–10853. (b) Teimouri, M. B.; Shaabani, A.; Bazhrang, R. *Tetrahedron* **2006**, *62*, 1845–1848. (c) Teimouri, M. B.; Bazhrang, R.; Eslamimanesh, V.; Nouri, A. *Tetrahedron* **2006**, *62*, 3016–3020.

(13) Selected physical and spectroscopic data for compound **5c**: Red powder (0.400 g, 95%); mp 232−235 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3250 (N−H), 1635 (C═O); δ_H (400.1 MHz, $CDCl_3$) 1.32−2.34 (10H, m, 5 CH_2), 3.95 (1H, m, N−C*H*), 7.14 (1H, d, *J* 7.3 Hz, N*H*), 7.39−8.48 (11H, m, arom. hydrogens); δ_C (100.7 MHz, $CDCl_3$) 190.24, 178.61, 164.72, 150.57, 141.31, 134.50, 131.90, 131.04, 130.94, 130.28, 130.16, 129.04, 128.52, 128.23, 127.44, 126.85, 126.30, 124.33, 122.63, 120.17, 119.86, 95.02, 51.75, 33.37, 25.41, 24.52; Anal. Calcd. for $C_{28}H_{23}NO_3$ (421.48): C, 79.79; H, 5.50; N, 3.32%. Found: C, 79.70; H, 5.53; N, 3.40%. Selected physical and spectroscopic data for compound **5h**: Purple powder (0.404 g, 92%); mp 195−197 °C; FT-IR (KBr) ($\nu_{max,}$ cm^{-1}): 3427 (N−H), 1618 (C═O); δ_H (400.1 MHz, $CDCl_3$) 1.56 (9H, s, CMe_3), 4.80 (1H, br s, N*H*), 7.25−8.64 (12H, m, arom. hyrdrogens and C*H*═C*H*); δ_C (100.7 MHz, $CDCl_3$) 181.34, 155.95, 151.45, 146.77, 134.83, 134.19, 133.20, 132.21, 130.34, 130.18, 129.65, 127.52, 126.76, 126.72, 126.36, 125.59, 125.30, 125.00, 124.65, 121.92, 120.58, 120.49, 98.56, 54.27, 30.45; Anal. Calcd. for $C_{27}H_{22}N_2O_4$ (438.47): C, 73.96; H, 5.06; N, 6.39%. Found: C, 74.04; H, 5.07; N, 6.22%.

(14) Sung, K.; Chen, C.-C. *Tetrahedron Lett.* **2001**, *42*, 4845–4848.

CC8000103