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Synthesis of 2,3,5-trisubstituted furans from α-formylaroylketene dithioacetals

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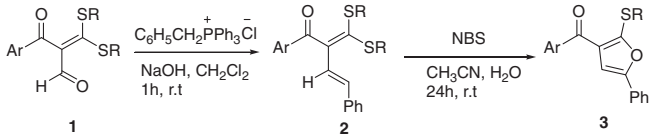
ABSTRACT

A new strategy for the synthesis of 2,3,5-trisbustituted furans from α-formylketene dithioacetals is described. The protocol involves a facile conversion of α-formylketene dithioacetals to vinylketene dithioacetals via Wittig reaction and subsequent *N*-bromosuccinimide-mediated cyclization to 2,3,5-trisbustituted furans. Further conversion of the 2-thioalkylfurans thus obtained to 2-aminofurans shows the potential synthetic utility of this new approach.

Furans are key structural units in many natural products,[1] pharmaceuticals[2] and a broad spectrum of biologically relevant synthetic molecules.[3] Extensive synthetic efforts have been devoted by various research groups on polysubstituted furans. Owing to their unique and versatile biological activities, there is a continuing interest in this area of heterocyclic synthetic chemistry. Paal–Knorr furan synthesis,[4] which is essentially an acid-catalyzed cyclocondensation of 1,4-dicarbonyl compounds or their equivalents, and Feist–Benary synthesis,[5] which involves condensation of β-dicarbonyl compounds with α-haloketones, are the most established general methods for the construction of furan ring. A number of strategies utilizing cycloisomerization of alkyne or allene containing acyclic precursors[6] and several novel annulation approaches, such as reactions of carbonyls with fluoropropargyl chloride,[7] aldehydes with allylic sulfoxides,[8] α,β-acetylenic ketones with α-diazo esters,[9] aldehydes with ketimines,[10] acyl chlorides with 2,3-bis(trimethylsilyl)buta-1,3-diene,[11] and Ag or Au catalyzed conversion of alkynyloxiranes[12] have recently been reported. Herein, we report a new strategy (Scheme 1) for the synthesis of 2,3,5-trisubstituted furans in a two-step process starting from α-formylaroylketene dithioacetals **1**, which we have previously demonstrated to be highly useful intermediates for the synthesis of a variety of heterocycles.[13–15]

The use of vinylketene dithioacetals as 1,3-dienes in Diels–Alder reactions has been extensively documented.[16] In line with these studies, we decided to explore the synthetic utility of our α-formylaroylketene dithioacetals **1**. Conversion of **1** to vinylketene dithioacetals **2** was accomplished via a simple Wittig reaction[17] in 78–90% yields (Table 1). But, unfortunately the dienes **2** failed to react in Diels–Alder reactions toward various dienophiles, such as maleic anhydride, dimethyl acetylene dicarboxylate, *p*-benzoquinone, etc. At this point, we presumed that a bromination reaction of the diene **2** followed by amination might be developed as a useful route toward the synthesis of trisubstituted pyrroles, which form key scaffolds in many inhibitors investigated in medicinal chemistry/pharmaceutical research.

Bromination reactions of the vinylketene dithioacetals **2** with bromine in THF, however, resulted in complex reaction mixtures with severe difficulty in isolating and characterizing any useful product. However, our previous experience on the use of *N*-bromosuccinimide (NBS) on polymer support for the α-bromination reactions of α-oxoketene dithioacetals[18] prompted us to investigate the possibility of brominating **2** with NBS. Thus the vinylketene dithioacetals **2** were treated with NBS in acetonitrile at room temperature for 24 h. Contrary to the expected bromo-adduct, we observed the formation of trisubstituted furans **3** as major products (Scheme 1 and Table 1).



Scheme 1. General scheme showing the conversion of α-formylaroylketene dithioacetals **1** to vinylketene dithioacetals **2** and subsequent *N*-bromosuccinimide-mediated conversion of **2** to 2,3,5-trisubstituted furans **3**.

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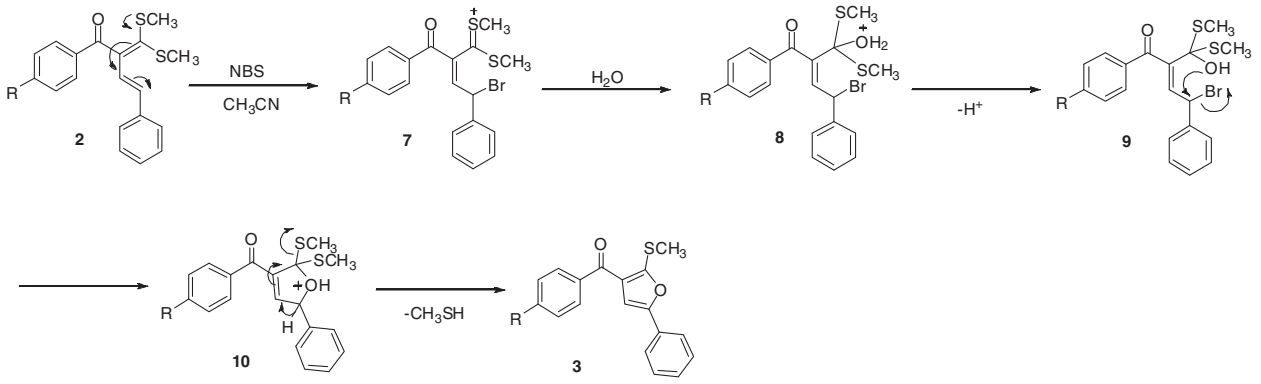
Table 1
Vinylketene dithioacetals **2a–g** and corresponding 2,3,5-trisubstituted furans **3a–g** (Scheme 1) and aminofurans **11a** and **11e** (Scheme 3)

Sl. No.	Ar	R	% Yield (**2**)[a]	% Yield (**3**) [b]	% Yield (**3**) (**11**)[c]
a	4-$OMeC_6H_4$	Me	90	70	95
b	C_6H_5	Me	83	63	–
c	4-ClC_6H_4	Me	85	66	–
d	4-BrC_6H_4	Me	80	64	–
e	4-$CH_3C_6H_4$	Me	86	65	94
f	4-$CH_3C_6H_4$	$CH_2C_6H_5$	82	63	–
g	C_6H_5	$CH_2C_6H_5$	78	60	–

[a] See Ref. 23 for the general procedure for the synthesis of these derivatives. See Supplementary data for spectral data.
[b] See Ref. 23 for the general procedure for the synthesis of these derivatives. See Supplementary data for spectral data.
[c] See Ref. 25 for the general procedure for the synthesis of these derivatives. See Supplementary data for spectral data.



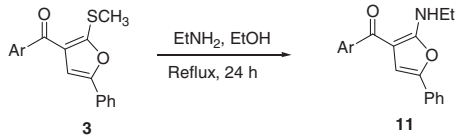
Scheme 2. Proposed mechanism for the formation of the 2,3,5-trisubstituted furans **3** from vinylketene dithioacetals **2**, mediated by *N*-bromosuccinimide.

A plausible mechanism for the formation of the furan is outlined in Scheme 2 below.

Similar to the polar mechanism for the formation of bromohydrins from simple alkenes,[19] bromination at C-4 carbon atom of the diene **2** by NBS might lead to the intermediate **7**, which undergoes hydrolysis followed by deprotonation to the key intermediate **9**. A subsequent nucleophilic substitution reaction of the bromine with the hydroxyl group on the C-1 carbon atom would result in the cyclic intermediate **10**, which is aromatized with the elimination of one molecule of methane thiol resulting in the formation of the 2,3,5-trisubstituted furan **3**. It should be noted that in this proposed mechanism, the hydrolysis of the intermediate **7** occurs prior to the aqueous work-up (quenching of the NBS reaction on ice-cold water)[24] although in-principle it could take place during the work-up as well. We, however, unfortunately could not detect the intermediate **7** in the GC–MS analysis of the crude reaction mixture (prior to work-up). Presumably this intermediate is short lived and most of its conversion to the final furan occurs relatively quickly (in a few minutes), although the reactions were run for longer time for isolating maximum yields.

We have subsequently explored the possibility of converting the newly prepared trisubstituted furan derivatives **3** to 2-aminofurans by replacing the thioalkyl group with alkylamino group. 2-Aminofurans have been reported to be useful intermediates in many natural product syntheses.[20–22] Thus **3** were treated with ethylamine in refluxing ethanol under the reaction conditions reported by Fu et al.[8] resulted in the amino derivatives **11** in excellent yield (Scheme 3).[25] This reaction also reveals the scope for further functionalizing/derivatizing the newly prepared furan derivatives.

In summary, we have developed an efficient method for the synthesis of 2,3,5-trisubstituted furans from an easily accessible and versatile synthetic intermediate α-formylketene dithioacetals. Further conversion of the 2-thioalkylfurans to highly useful synthetic intermediate 2-aminofurans shows the potential utility of this new approach in natural product synthesis. We believe that this new method would be highly useful in a range of research and pharmaceutical development endeavors. Detailed investigations on the applications of this new strategy in medicinal chemistry as well as detailed mechanistic investigations are in progress and will be reported in due course.



Scheme 3. Synthesis of 2-aminofurans from 2-thiomethylfurans.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.128.

References and notes

1. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819.
2. Hou, X.-L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2003**, *15*, 167–205.
3. (a) Lukevits, E.; Demicheva *Chem. Heterocycl. Compd.* **1993**, *29*, 243–267; (b) Perrier, L.; Bayly, C.; Laliberté, F.; Huang, Z.; Rasori, R.; Robichaud, A.; Girard, Y.; Macdonald, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 323–326; (c) Mortensen, D. S.;

Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 3838–3848.
4. Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277–5288. and references cited therein.
5. Mross, G.; Holtz, E.; Langer, P. *J. Org. Chem.* **2006**, *71*, 8045–8049.
6. Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868–9878.
7. Xu, B.; Hammond, G. B. *J. Org. Chem.* **2006**, *71*, 3518–3521.
8. Fu, Z.; Wang, M.; Ma, Y.; Liu, Q.; Liu, J. *J. Org. Chem.* **2008**, *73*, 7625–7630.
9. Zhao, L.-B.; Guan, Z.-H.; Han, Y.; Xie, Y.-X.; He, S.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 10276–10278.
10. Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376–12377.
11. Babudri, F.; Cicco, S. R.; Farinola, G. M.; Lopez, L. C.; Naso, F.; Pinto, V. *Chem. Commun.* **2007**, 3756–3758.
12. Blank, A.; Tenbrink, K.; Weibel, J. M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342–5348.
13. Mathews, A.; Asokan, C. V. *Tetrahedron* **2007**, *63*, 7845–7849.
14. Mathews, A.; Anabha, E. R.; Sasikala, K. A.; Lethesh, K. C.; Krishnaraj, K. U.; Sreedevi, N. K.; Prasanth, M.; Devaky, K. S.; Asokan, C. V. *Tetrahedron* **2008**, 1671–1675.
15. Anabha, E. R.; Asokan, C. V. *Synthesis* **2006**, 0151–0155.
16. Gupta, A. K.; Ila, H.; Junjappa, H. *Tetrahedron* **1989**, *45*, 1509–1516.
17. (a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44; (b) Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318.
18. Mathew, P. *Ph.D. Thesis*, Mahatma Gandhi University, Kerala, India, 2004.
19. Beger, J.; Haufe, G.; Alvernhe, G.; Laurent, A.; Ernet, T.; Goj, O.; Kroger, S.; Sattler, A. *J. Prakt. Chem.* **1991**, *333*, 677–698.
20. Nair, V.; Vinod, A. U. *Chem. Commun.* **2000**, 1019–1020.
21. Alizadeh, A.; Rostamnia, S.; Hu, M.-L. *Synlett* **2006**, 1592–1594.
22. Alizadeh, A.; Rostamnia, S.; Zoreh, N.; Oskueyan, Q. *Synlett* **2007**, 1610–1612.
23. *General procedure for the synthesis of (E)-2-(bis(alkylthio)methylene)-1-aryl-4-phenylbut-3-en-1-ones*: The appropriate 2-aroyl-3,3-bis(alkylthio)-acrylaldehyde (1 mmol) dissolved in DCM (15 mL) was stirred with triphenylbenzyl phosphonium chloride (0.39 g, 1 mmol) for 5 min at room temperature. To this was added 50% aqueous NaOH (7.5 mL) solution slowly and the mixture was stirred further for 1 h at room temperature. The reaction mixture was then poured onto ice-cold water (20 mL). A semi-solid obtained was extracted with DCM (3×25 mL), the organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated off. The crude product obtained was purified by column chromatography on silica gel (60–120 mesh) using ethyl acetate–hexane (1:19) mixture as the eluent to get **2a–g** in 78–90% yield as pale yellow crystalline solid.
24. *General procedure for the synthesis of aryl-(2-(alkylthio)-5-phenylfuran-3-yl)methanones from (E)-2-(bis(alkylthio)methylene)-1-aryl-4-phenylbut-3-en-1-ones*: A solution of (*E*)-2-(bis(alkylthio)methylene)-1-aryl-4-phenylbut-3-en-1-ones (1 mmol) and NBS (264 mg, 1.5 mmol) in aqueous acetonitrile (5 mL) was stirred at room temperature for 24 h. The reaction mixture was poured onto ice-cold water and extracted with dichloromethane (2×20 mL). The organic layer was dried with anhydrous sodium sulfate, the solvent was removed under vacuum and the crude product obtained was purified by column chromatography on silica gel (60–120 mesh) using hexane as the eluent to get **3a–g** in 60–70% yield as white solid.
25. *General procedure for the synthesis of (2-(ethylamino)-5-phenylfuran-3-yl)(aryl)methanones from aryl-(2-(alkylthio)-5-phenylfuran-3-yl)methanones*: To a solution of aryl-(2-(alkylthio)-5-phenylfuran-3-yl)methanones (1 mmol) in ethanol (5 mL) was added ethylamine (0.2 mL, 3 mmol) and the reaction mixture was refluxed for 24 h. The reaction mixture was then poured onto saturated sodium chloride solution (40 mL), neutralized with saturated $NaHCO_3$ and extracted with dichloromethane (3×25 ml). The organic layer was washed with water (2×20 mL), dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel (60–120 mesh) using hexane/ethyl acetate (40:60) as the eluent to get **11a** and **11e** in 94–95% yield as pale yellow solid.