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A sequential synthesis of substituted furans from aryl alkynes and ketones involving a cerium(IV) ammonium nitrate (CAN)-mediated oxidative cyclization

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ABSTRACT

A convenient, two-step synthesis of substituted furans from readily available aryl alkynes and ketones is reported. The furan-forming oxidative cyclization is mediated by the combination of cerium(IV) ammonium nitrate and potassium bromide and can be carried out in an open flask.

Furans constitute a ubiquitous class of heterocycles widely found in a variety of biologically active natural products and man-made molecules alike.[1] The furan unit is also a versatile building block for the synthesis of various cyclic and acyclic compounds.[2] They also form key structural units which impart the desired properties in functional materials.[3] As a consequence, the synthesis of substituted furans has attracted a lot of attention.[4] The cyclocondensation of 1,4-dicarbonyl compounds, known as the Paal–Knorr furan synthesis is one of the oldest and most widely used methods for the construction of 2,5-disubstituted furans. Paal–Knorr synthesis often involves the use of strong acids and harsh conditions such as microwave heating.[5] Transition-metal mediated cycloisomerization of alkynyl and allenyl substrates bearing a suitably placed oxa-substituent is an important modern method for furan synthesis.[6] The synthesis of unsymmetrically substituted furans, however, requires non-trivial, multi-step assembly of the appropriate 1,4-dicarbonyl compound[1c] (Paal–Knorr) or the oxa-alkyne/allene(cycloisomerization).[6c] In this context, a two-step synthesis of 2,5-diarylfurans from aryl alkynes and alcohols developed by Beller, Dixneuf, and co-workers is noteworthy (Scheme 1, Eq. 1).[7] This method employs sequential ruthenium and copper catalysis and 2,5-diarylfurans are generated from readily available aryl alkynes. However, only symmetrically substituted 2,5-diarylfurans can be accessed by this method which requires the use of a rather expensive ruthenium catalyst.

Recently, Trofimov and co-workers reported a superbase-promoted α-vinylation of ketones using aryl alkynes.[8] The reaction affords β,γ-unsaturated ketones **3** (Scheme 1, Eq. 2) which remarkably, do not isomerize to the α,β-unsaturated analogs and thereby offer avenues for annulations[9] involving the ketone oxygen functionality and the olefin unit. We surmised that such an annulation reaction may be triggered by electrophilic activation of the olefin moiety in **3**. Our studies along this direction using halogen electrophiles culminated in the development of an operationally simple and sequential synthesis of substituted furans **4** (Scheme 1, Eq. 2). The results of our investigations are presented in the following sections.

The β,γ-unsaturated ketone **3a** prepared from phenyl acetylene and acetophenone was subjected to treatment with various halogen electrophiles. Initially, a one-pot approach was explored wherein the halogen-containing reagents were added to the reaction mixture containing **3a** directly. Addition of N-bromosuccinimide gave no reaction whereas addition of iodine resulted in the formation of a number of unidentified products (Table 1, entries 1–2). Nair has reported that the combination of potassium bromide and cerium(IV)ammonium nitrate (CAN) is a convenient and efficient means to brominate alkenes.[10] This method, when employed as a one-pot procedure, afforded 2,5-diphenylfuran **4a** as the only isolable product in low yields (entry 3). Pleasingly, an isolated sample of **3a** reacted with CAN-KBr combination to afford the furan **4a**

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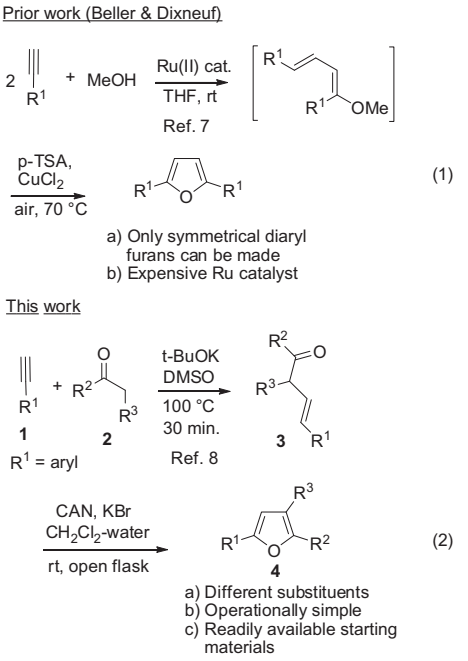
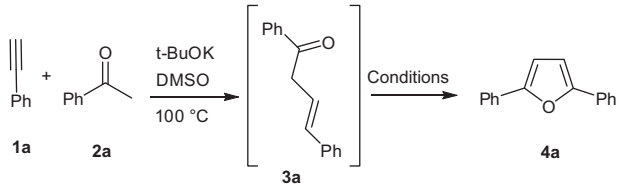


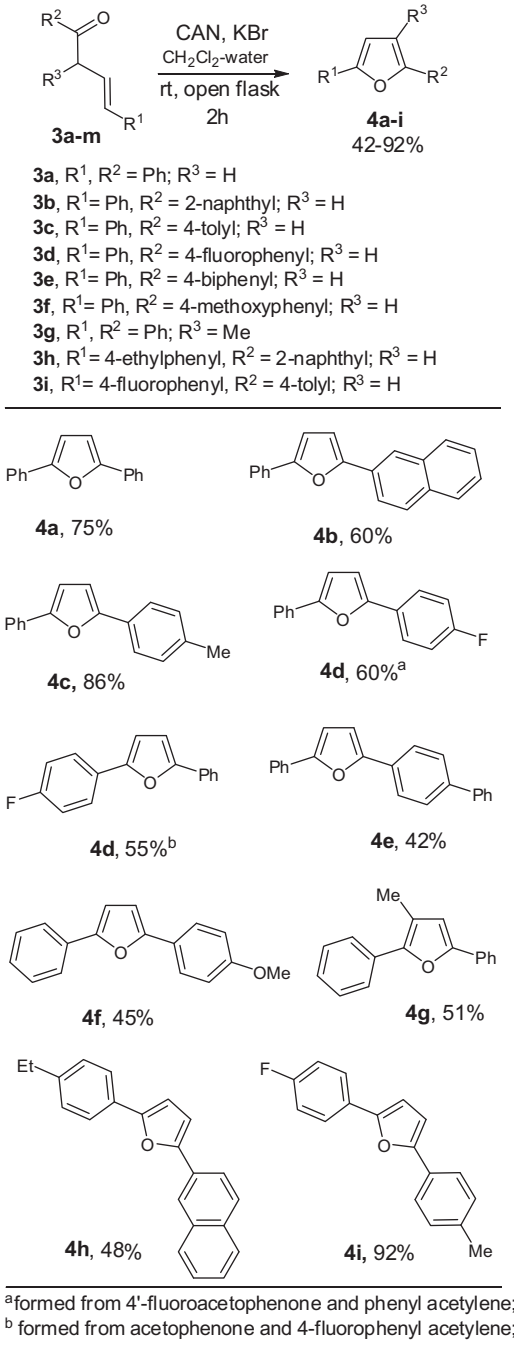
Scheme 1. Synthesis of 2,5-disubstituted furans from alkynes.

Table 1
Reaction of β,γ-unsaturated ketone **3a** with electrophilic halogen sources



No.	Conditions	Yield/result
1[a]	1.5 equiv NBS, rt, 12 h	No reaction
2[a]	1.5 equiv I_2, rt, 12 h	Unidentified products
3[a]	3.0 equiv CAN, 3.0 equiv KBr, rt, 2 h	10% (**4a**)
4[b]	1.5 equiv CAN, 1.5 equiv KBr, rt, 2 h	49% (**4a**)
5[b]	2.0 equiv CAN, 2.0 equiv KBr, rt, 2 h	69% (**4a**)
6[b]	3.0 equiv CAN, 3.0 equiv KBr, rt, 2 h	75% (**4a**)
7[b]	2.3 equiv CAN, rt, 12 h	Mostly **3a**
8[b]	1.5 equiv Br_2, CH_2Cl_2, rt, 6 h	21% (**4a**)
9[b]	0.1 equiv p-TSA, 0.1 equiv $CuCl_2$, Toluene, O_2, 70 °C	35% (**4a**)

[a] One-pot operation starting from **1a** and **2a** in DMSO.
[b] Reactions carried out with isolated **3a** in CH_2Cl_2-water.



[a] formed from 4'-fluoroacetophenone and phenyl acetylene;
[b] formed from acetophenone and 4-fluorophenyl acetylene;

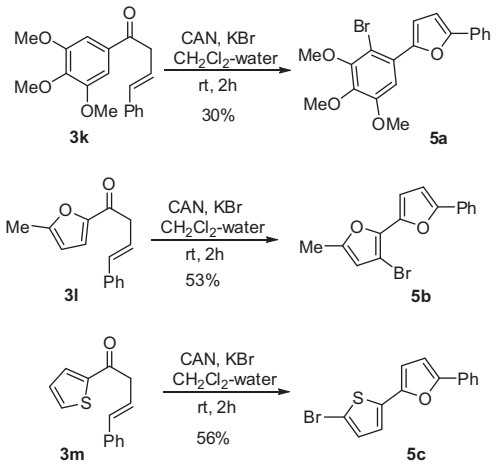
Scheme 2. Sequential synthesis of substituted furans; yields of isolated products listed.

in 75% yield under optimized conditions (entry 6).[11] Since the furan **4a** was the outcome of an oxidative cyclization of **3a** and contained no bromine, the reaction was attempted in the absence of KBr, however, without success (entry 7). Furan **4a** was obtained in low yield along with unidentified side products when **3a** was treated with bromine (entry 8) as well as when **3a** was subjected to the conditions of oxidative cyclization as reported by Beller[7] (entry 9).

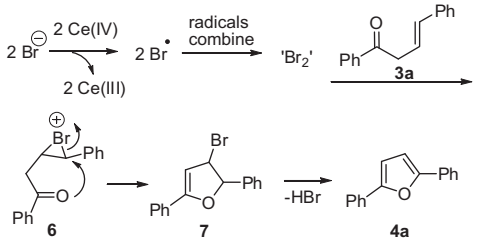
The generality and scope of the furan synthesis was then explored under the optimized reaction conditions. An assortment of β,γ-unsaturated ketones **3a**–**m** was prepared[8a,b,12] and subjected to the oxidative cyclization. The results are summarized in Scheme 2.

The oxidative cyclization reaction seems to be quite general as it proceeded readily to afford a variety of 2,5-disubstituted furans **4a**–**i**. The combination of phenylacetylene/4′-fluoroacetophenone and 4-fluorophenylacetylene/acetophenone afforded the same 4-fluorophenyl bearing furan **4d**. The trisubstituted furan **4g** is accessible in two steps from propiophenone and phenylacetylene. Aryl-substituted phenylacetylenes could also be successfully employed in the sequential synthesis to furnish the 2,5-diarylfuran derivatives **4d**, **h**, **i**.

Interestingly, the oxidative cyclization was followed by site-selective ring bromination in a few cases (Scheme 3). β,γ-Unsaturated ketones (**3k**–**m**) underwent oxidative cyclization and ring bromination under the reaction conditions to afford the products



Scheme 3. Tandem oxidative cyclization-ring bromination of electron rich substrates.



Scheme 4. A mechanistic hypothesis for oxidative cyclization.

5a–c. For example, the highly electron rich trimethoxyphenyl unit of **3l** was brominated selectively to afford the product **5a**. The ^{1}H NMR spectrum of **5a** exhibited resonances corresponding to the furan hydrogens as mutually coupled (J = 3.4 Hz) doublets at δ 7.22 and 6.79. The singlet resonance at δ 7.25 is attributed to the lone hydrogen on the bromo-trimethoxyphenyl ring. In the ^{13}C NMR, the bromine-carrying carbon resonated at δ 107.2. Similarly, in the ^{1}H NMR spectrum of **5b**, two mutually coupled doublets of the central furan ring were observed at δ 6.81 and 6.72. The lone hydrogen on the methylfuran ring resonated as a multiplet at δ 6.14–6.13 due to coupling with the methyl group on the adjacent carbon. Additionally, the bromine-bearing carbon resonated at δ 95.9 in the ^{13}C NMR spectrum.

It is notable that the cyclization-bromination sequence observed in **3k–m** is selective in two ways. Bromine is incorporated on only one out of the two aryl rings of **3k–m** (trimethoxyphenyl, methylfuranyl, and thienyl). It is clear that these rings are significantly electron rich (compared to the other phenyl ring) and this observation conforms to the known propensity of CAN to promote ring iodination of electron rich aromatic compounds.[13] Additionally, the site selectivity of bromination in **3l–m** is also noteworthy.

The exact mechanistic details of the oxidative cyclization are not clear at this stage, however, a rationalization can be made as follows. A comparison of the redox potentials of the $Br^-/Br^\cdot$ (1.03 V vs NHE) and Ce(IV)/Ce(III) (1.61 V vs NHE) systems indicate that the cerium(IV)-mediated oxidation of bromide anion to bromine radical is presumably the initial event.[10] The bromine radicals combine to produce 'nascent' molecular bromine which reacts with the olefin in **3a**. The benzylic carbon of the resultant bromonium ion **6** is suitably placed to interact with the oxygen end of the ketone functionality. This cyclization is followed by aromatization via loss of HBr to afford the furan **4a** (Scheme 4). It is important to note that atmospheric oxygen does not interfere in the reaction even though it is carried out in an open flask. Additionally, when the reaction was run separately in the presence of radical scavengers (TEMPO and *p*-benzoquinone) no significant decrease in the yield of the product **4a** was observed (69% and 74%, respectively compared to 75% in the absence of radical scavenger). These observations suggest that the involvement of any carbon-centered radical (formed by the addition of bromine radical to the olefin in **3a**) may be ruled out. The site-selectivity of bromination in **5b–c** indicates that the aromatic bromination most likely proceeds after the furan ring is formed (the keto group present in **3l–m** should disfavor the bromination at the observed positions).

In conclusion, a facile and operationally simple synthetic route to furans has been developed. A variety of substituted furans can be accessed in two steps from commercially available aryl alkynes and ketones thus alleviating the need for a lengthy substrate synthesis. Moreover, the oxidative cyclization can be run in aqueous dichloromethane in an open flask. The 2,5-diarylfuran unit present in **4a–i** is an important structural fragment found in a number of anticancer[14] and anti-inflammatory[1d] compounds. Additionally, the products **5a–c** of the site-selective bromination offer synthetic opportunities for further functionalization of the aryl rings via the well-established metal-mediated coupling reactions of bromoarenes.[15]

Efforts to apply this method in the synthesis of a library of furans for medicinal chemistry applications and extension of this methodology to pyrrole synthesis are currently underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedure, product characterization and ^{1}H and ^{13}C NMR spectra for all the new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.039.

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11. *Typical experimental procedure for the oxidative cyclization reaction of* ***3a****:* A solution of CAN (1.64 g, 3 mmol) in distilled water (5 mL) was added dropwise to a suspension of the β,γ-unsaturated ketone **3a** (222 mg, 1 mmol) and KBr (355 mg, 3 mmol) in dichloromethane (10 mL) in an open flask at room temperature. When the reaction was complete (TLC analysis), it was diluted with water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on silica gel using petroleum ether as eluent to afford 2,5-diphenylfuran **4a**[16] as a white solid (165 mg, 75%). mp 83–84 °C (CH_2Cl_2-hexane); IR (KBr) ν_{max}: 3037, 1610, 1488, 1479, 1469, 1447, 1156, 1079, 1024, 927, 911, 795 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76–7.74 (4H, m), 7.43–7.39 (4H, m), 7.29–7.26 (2H, m), 6.75 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 130.7, 128.7, 127.3, 123.7, 107.2; HRMS calcd for $C_{16}H_{12}O$ 220.0888; found 220.0886.
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