An Efficient Access to Fluorescent 2,3,4-Tricyanofurans from α-Cyano Ketones Using DDQ as Maleonitrile Building Block

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Abstract: An efficient synthetic method was developed for the synthesis of 2,3,4-tricyanofurans from α-cyano ketones using DDQ as maleonitrile building block under very mild conditions. This methodology allows for the construction of a new kind of fluorescent core framework.

Key words: furans, cyano ketones, DDQ, cyclization, fluorescent cores

Furans are not only an important class of heterocycles prevalent in natural products, pharmaceuticals, flavors, and agrochemicals but also versatile intermediates in organic synthesis.[1] Up to date, myriad approaches to access furans are well documented.[2] Generally, they can be categorized into three main strategies. The first involves the direct functionalization of the existing furan rings using Heck, Stille, Suzuki, and Negishi coupling reactions.[2b] However, the corresponding tin, silicon, and boron intermediates are not easy to access, although direct oxidative coupling based on C–H and C–halogen bond activation has been achieved.[3] The second relates to the construction of ring itself from acyclic precursors[2a,c] such as 1,4-diketones, alkyne-containing substrates or their equivalents, which necessitates the complicated functionalization of basic chemical materials. The third is the one-pot synthesis of the furan scaffold from easily accessible substrates without prefunctionalization.[4] Due to its high atom-economy, operational ease, and good availability, this synthetic strategy has proven to be one of the most attractive methods; however, the known reports are very limited.[4,5]

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a well-known dehydrogenative oxidizing reagent in organic synthesis[6] and has been successfully used for constituting new C–C and C–heteroatom bonds via C–H activation.[7] To the best of our knowledge, however, DDQ rarely serves as reactant precursor.[8] The importance of fluorescent molecules has been well documented in various fields of research.[9] The use of new synthetic methodologies to discover novel fluorescent core frameworks has attracted great interest.[10] Herein, we wish to report a facile and efficient methodology for the construction of the
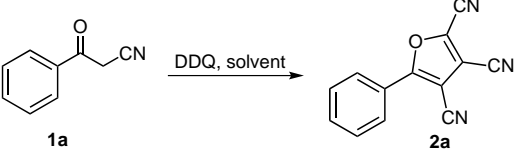
furan scaffold using DDQ as maleonitrile building block (Scheme 1) and a surprising discovery of a new series of fluorescent core frameworks.

Initially, the reaction of 2-cyanoacetophenone (**1a**) with DDQ was used as the model to optimize the reaction parameters. The results are summarized in Table 1. Treatment of **1a** with DDQ was firstly performed in acetonitrile at room temperature. With 3.0 equivalents of DDQ being used, the reaction went smoothly to completion, furnishing 2,3,4-tricyano-5-phenylfuran (**2a**) in 81% yield (Table 1, entry 1). When the equivalents of DDQ were lowered to 2.5, 2.0, and 1.2, the ketone **1a** remained partly unfinished and the product **2a** was obtained in the yield of 76%, 51%, and 30%, respectively (Table 1, entries 2–4). Furthermore, several other solvents including dichloromethane, benzene, ethyl acetate, nitromethane, and ethanol were tested for this transformation (Table 1, entries 5–9). To our delight, all tested solvents except ethanol gave good yields. The use of acetonitrile and ethyl acetate gave a similar yield (81% vs. 80%). Considering the cost and environmental friendliness, ethyl acetate was chosen as the best solvent for this transformation.
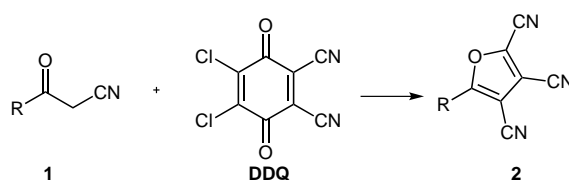
Scheme 1 Synthesis of 2,3,4-tricyanofurans using DDQ

With the optimized conditions in hand, we set out our investigations into the scope of the annulation of various α-cyano ketones with DDQ, and the results are summarized in Table 2.[11] All the tested substrates including aryl and aliphatic ketones reacted well to give the corresponding furans in moderate to good yields (28–87%). For aryl ketones, those bearing electron-releasing and electron-withdrawing groups underwent smoothly. In spite of this, subtle electronic effects were observed. For example, electron-withdrawing groups gave higher yields (Table 2, entries 2 and 4), while the presence of electron-rich groups decreased the selectivity and offered lower yields (Table 2, entries 8–11). Evidently, the electron-rich aromatic ring competed with α-CH$_2$ in molecules **1**, making

Table 1 Optimization of the Reaction Conditions[a]

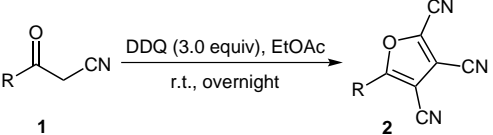| Entry	DDQ/**1a**[b]	Solvent[c]	Yield (%)[d]
1	3.0	MeCN	81
2	2.5	MeCN	76
3	2.0	MeCN	51
4	1.2	MeCN	30
5	3.0	CH_2Cl_2	77
6	3.0	benzene	75
7	3.0	EtOAc	80
8	3.0	$MeNO_2$	68
9[e]	3.0	EtOH	20

[a] **1a** (0.5 mmol) was treated with DDQ at 25 °C overnight.
[b] Molar ratio.
[c] Dried using standard methods.
[d] Isolated yield.
[e] Unidentified contaminant dominates.

the reaction more complicated (giving unidentified impurities). Also, steric effects were found. When the substituents such as chloro or methyl group were on the *ortho* position of the aromatic ring, the reaction gave lower yield (Table 2, entries 3 and 7). Notably, the halo groups were well tolerated under annulation conditions, which allows for the derivation of the furans via the palladium- or copper-catalyzed coupling reactions reported previously.[12] Besides, this transformation worked well not only with electron-rich furyl ketone but also with the enone derived from cinnamic acid (Table 2, entries 12 and 13).

To assess whether radical species are formed in this reaction, the radical scavenger TEMPO was employed (Scheme 2). The reactions are completely inhibited by six equivalents of TEMPO. This result indicates that such a transformation may involve radical intermediates.
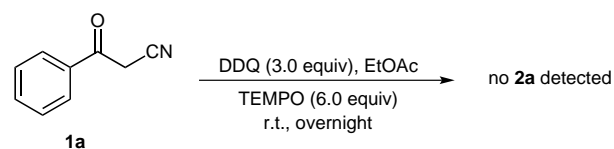

Scheme 2 Radical-trapping experiment

The mechanism for this protocol is yet unknown, but it is presumably subjected to single electron transfer (SET) cycloaddition and subsequent retro-Diels–Alder reaction, eventually giving out 2,3-dichloromaleic anhydride (Scheme 3). This resulting anhydride was identified by

Table 2 Syntheses of 2,3,4-Tricyanofurans with DDQ[a]

Entry	Product	**1** R	Yield (%)[b]
1	**2a**	Ph	80
2	**2b**	$4\text{-}ClC_6H_4$	87
3	**2c**	$2\text{-}ClC_6H_4$	72
4	**2d**	$4\text{-}BrC_6H_4$	83
5	**2e**	$4\text{-}MeC_6H_4$	63
6	**2f**	$3\text{-}MeC_6H_4$	60
7	**2g**	$2\text{-}MeC_6H_4$	56
8	**2h**	$4\text{-}MeOC_6H_4$	42
9	**2i**	$2\text{-}MeOC_6H_4$	45
10	**2j**	$2,4\text{-}(MeO)_2C_6H_3$	32
11	**2k**	$3,4\text{-}(MeO)_2C_6H_3$	28
12	**2l**	furyl-2	45
13	**2m**	$(E)\text{-}C_6H_4CH{=}CH$	63
14	**2n**	Me	77

[a] Reaction conditions: ketones **1** (0.5 mmol), DDQ (1.5 mmol), stirred in EtOAc at 25 °C overnight.
[b] Isolated yield.

NMR and GC–MS (see Figure S1 in the Supporting Information). Moreover, this speculation can be rationalized by the fact that the use of a cold 5% $NaHCO_3$ solution to wash the reaction mixture can give almost pure corresponding furans. The annulation was also proven by the X-ray molecular structure **2a** (Figure 1).
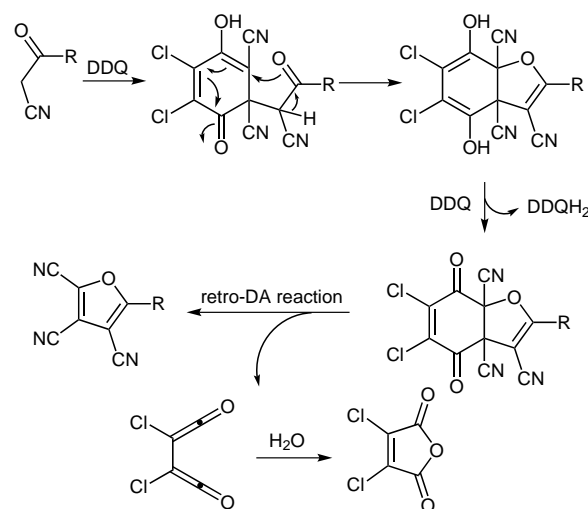
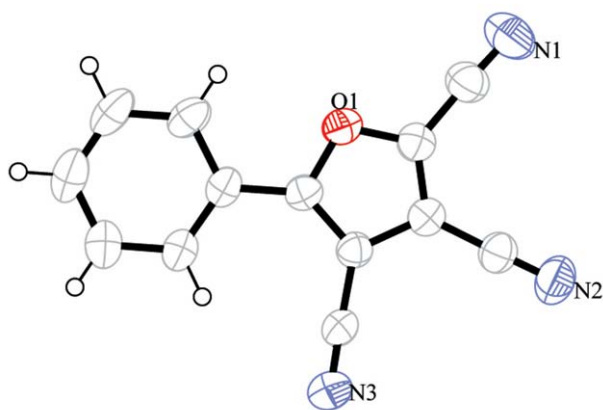**Scheme 3** Proposed mechanism for the annulation

Figure 1 ORTEP representation of **2a**

It is worth mentioning that 5-aryl-substituted 2,3,4-tricyanofurans were found to exhibit significantly strong photonic fluorescence both in solution and in solid state (see Figure S2 in the Supporting Information). Moreover, their photophysical properties can be tuned by changing the substituents of 5-position phenyl ring. Compounds **2b** and **2d** can be readily converted by the known metal-catalyzed coupling with *N,N*-dialkylamines to mimic a 'push–pull' π-electron mode.

In summary, we have developed a facile and efficient synthetic pathway that allows the construction of 5-substituted 2,3,4-tricyanofurans in moderate to good yields and good functional-group tolerance. More importantly, this approach has resulted in the discovery of a library of fluorophores. The application of this protocol, modification of such fluorescence core framework, and investigation of 2,3,4-tricyanofurans as fluorescence probes are currently ongoing.

Acknowledgment

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **Experimental Procedure**
DDQ (341 mg, 1.5 mmol) was added to α-cyano ketone (0.5 mmol) in EtOAc (2 mL). The resulting reaction mixture was stirred overnight during which time a yellow solid precipitated. EtOAc (30 mL) was added, and the resultant mixture was subsequently washed with cold aq 5% NaHCO₃ (3 × 10 mL) and brine. Silica gel (0.5 g) was added and the mixture rotary evaporated. The resulting powder was added to the top of a short silica gel column and purified using PE–EtOAc in a 10:1 to 7:1 ratio (v/v) as the eluent to afford the desired product.

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