RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2021, **11**, 18246

A computational study for the reaction mechanism of metal-free cyanomethylation of aryl alkynoates with acetonitrile†

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A computational study of metal-free cyanomethylation and cyclization of aryl alkynoates with acetonitrile is carried out employing density functional theory and high-level coupled-cluster methods, such as coupled-cluster singles and doubles with perturbative triples [CCSD(T)]. Our results indicate that the reaction of aryl alkynoates with acetonitrile in the presence of *tert*-butyl peroxybenzoate (TBPB) under metal-free conditions tends to proceed through cyanomethylation, spirocyclization and ester migration of the kinetically favoured coumarin derivatives. 1,2-Ester migration in the spiro-radical intermediate **10** does not proceed *via* the formation of the carboxyl radical **11** suggested by Sun and co-workers. Our results also demonstrate that the *t*-butoxy radical is substantially responsible the formation of the cyanomethyl radical by the abstraction of a hydrogen atom from acetonitrile.

Received 2nd March 2021
Accepted 12th May 2021

DOI: 10.1039/d1ra01649k

rsc.li/rsc-advances

Introduction

Cyanomethylation is a very useful reaction to synthesize cyano-containing compounds in medicinal and synthetic organic chemistry due to easy conversion of the cyano group into primary amines, ketones, carboxylic acids, esters, amides and even tetrazoles.[1–3] In addition, cyanomethyl moieties obtained *via* cyanomethylation are found as versatile motifs in some important bioactive natural products and drugs.[4,5] A variety of protocols have been reported, including transition-metal-catalyzed methods[6–16] and metal-free catalyzed methods[17–22] for the synthesis of cyanomethyl-containing compounds. Compared to the toxic metal used, metal-free catalyzed methods used acetonitrile[9–12,17,18] and its analogs such as bromoacetonitrile,[13–16] cyanoacetic acid[19,20] and ethyl cyanoacetate[5] have drawn considerable attention due to its inexpensive and environmental-friendly properties. In recent years, metal-free cyanomethylation using of acetonitrile as a cyanomethyl source in the synthesis of the cyano-containing compounds was reported.[17,18,21] In 2016, Sun and co-workers[18] demonstrated a convenient and efficient method for the synthesis of 3-cyanomethylated coumarins, a class of very important heterocyclic compounds in pharmaceuticals and dyes, *via* cyanomethylation and cyclization of aryl alkynoates using acetonitrile as the cyanomethyl source in the presence of *tert*-butyl peroxybenzoate (TBPB) under metal-free conditions. A control experiment carried out in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) showed that the thermal cyanomethylation and cyclization of aryl alkynoates proceeds *via* a radicalic process as described in Scheme 1.

According to the mechanism proposed by Sun and co-workers,[18] at first, TBPB (**1**) decomposed into the benzoyloxy (**2**) and *tert*-butoxy radical (**3**) at high temperature. One of these radicals abstracted a hydrogen atom from acetonitrile (**4**) to generate the cyanomethyl radical (**5**). An electrophilic attack of cyanomethyl radical (**5**) to alkynoate (**8**) yields the alkenyl radical **9**. Then, an intramolecular spirocyclization of the alkenyl radical **9** gives the spiro-radical intermediate **10**. Next, the ester migration took place *via* a carboxyl radical **11** to yield the radical **12**. Finally, the radical **12** was oxidized to a carbocation or a radical followed by deprotonation or abstraction of a hydrogen radical to yield the cyano-containing coumarin derivatives **13**. Additionally, in these reactions, benzoic acid (**6**) and *tert*-butanol (**7**) are also formed as by-product.

Result and discussion

Our results for the mechanism proposed by Sun and co-workers are reported in Fig. 1 and 2. For the initiation of the radicalic process, the **1** → **2** + **3** conversion, the computed reaction free energy is 30.8 kcal mol^{-1} (Fig. 1). Zhou[23] was reported that the bond dissociation energy (BDE) (Gibbs free energy at 383.15 K) of TBPB is 11.2 kcal mol^{-1} at M06-L-D3/6-31+G(d,p) level and no any transition state (TS) for this step. We did not also find any TS for this step. The decomposing of TBPB (1) into benzoyloxy

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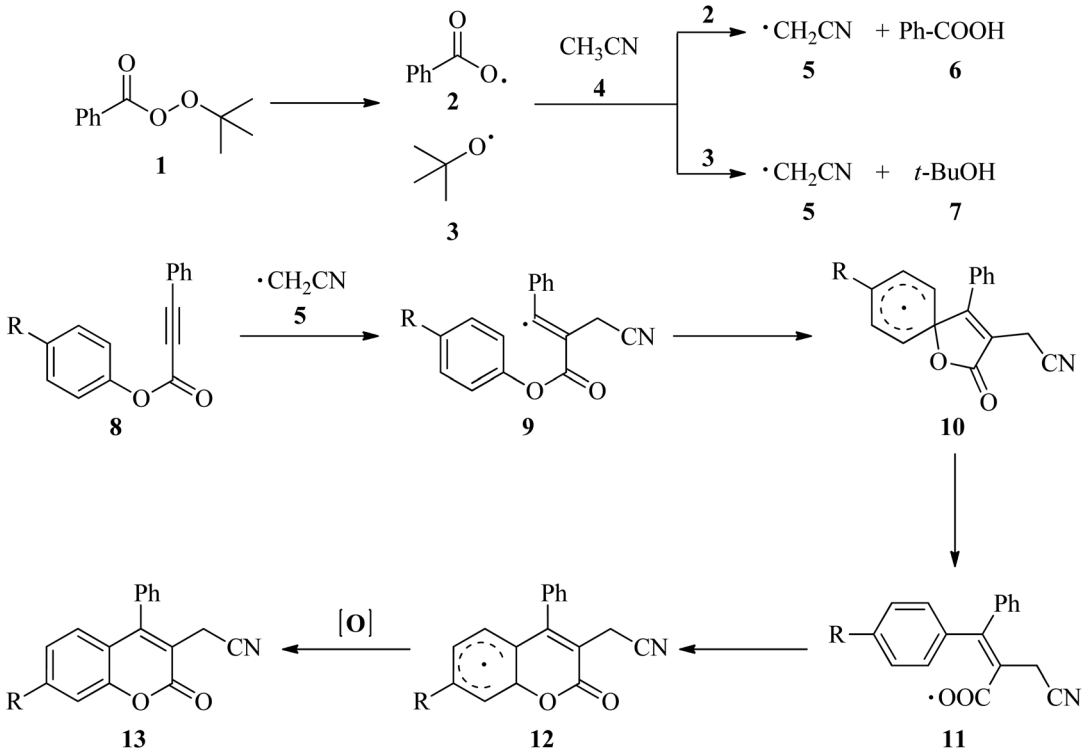
† Electronic supplementary information (ESI) available: Optimized geometries of the transition states with selected interatomic distances, Cartesian coordinates for computed structures. See DOI: 10.1039/d1ra01649k



Scheme 1 Proposed mechanism by Sun and co-workers.[18]

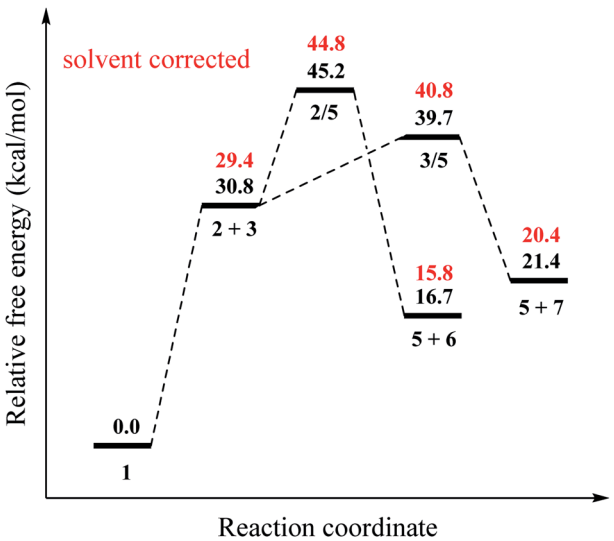


Fig. 1 Relative free energy profile (at 403.15 K) for the formation of cyanomethyl radical (**5**) shown in Scheme 1 at the DLPNO-CCSD(T)/cc-PVTZ//B3LYP-6-311G(d,p) level.

(**2**) and *t*-butoxy radical (**3**) was carried out at high temperature, which provide enough energy for this dissociation process. To generating the cyanomethyl radical (**5**), a hydrogen atom from acetonitrile (**4**) is abstracted by one of these radicals. For the abstraction of a hydrogen atom from acetonitrile (**4**) by benzoyloxy radical (**2**), **2** → **5**, the reaction free energy and barrier are −14.1 and 14.4 kcal mol^{-1}, respectively. For the other path for the formation of cyanomethyl radical (**5**), **3** → **5**, the reaction free energy and barrier are −9.4 and 8.9 kcal mol^{-1}, respectively. The barrier of the abstraction of a hydrogen atom from acetonitrile (**4**) by *t*-butoxy radical (**3**) is 5.5 kcal mol^{-1} lower than that of benzoyloxy radical (**2**) (Fig. 1). These results show that *t*-butoxy radical (**3**) is substantially responsible the abstraction of hydrogen atom.

In the literature, there are many studies for the reaction of aryl alkynotes with a variety of radicals. As a result of these studies, coumarin derivatives (**13** (ref. 18 and [24–35]) or **16** (ref. 36–45)) or styrene derivatives (**21** (ref. 46–48) or **22** (ref. 49)) were obtained under different reaction conditions. All plausible mechanism for aryl alkanoates **8** with cyanomethyl radical (**5**) is proceed as described in Scheme 2. There are two possible electrophilic attack of cyanomethyl radical (**5**) to the C–C triple bond of aryl alkynoate derivatives **8**. In the first one, the cyanomethyl radical (**5**) is reacted with alkynes, **8**, to form the intermediate **9**. The alternative electrophilic attack of cyanomethyl radical (**5**) to alkynes, **8**, is formed the intermediates **14**. For the electrophilic attack of cyanomethyl radical (**5**) to the C–C triple bond of aryl alkynoate derivative **8a**, **8a** → **9a**, the reaction free energy and barrier are −24.2 and 6.9 kcal mol^{-1}, respectively. For the alternative electrophilic attack of cyanomethyl radical (**5**) to the alkyne **8a**, **8a** → **14a**, the reaction free energy and barrier are −12.6 and 10.5 kcal mol^{-1}, respectively. Both the intermediate **9a** is more stable than the intermediate **14a** (the relative energy of **9a** is lower 11.6 kcal mol^{-1} than that of **14a**) and the barrier for the formation of **9a** is lower 3.6 kcal mol^{-1} than the barrier for the formation of **14a**. This

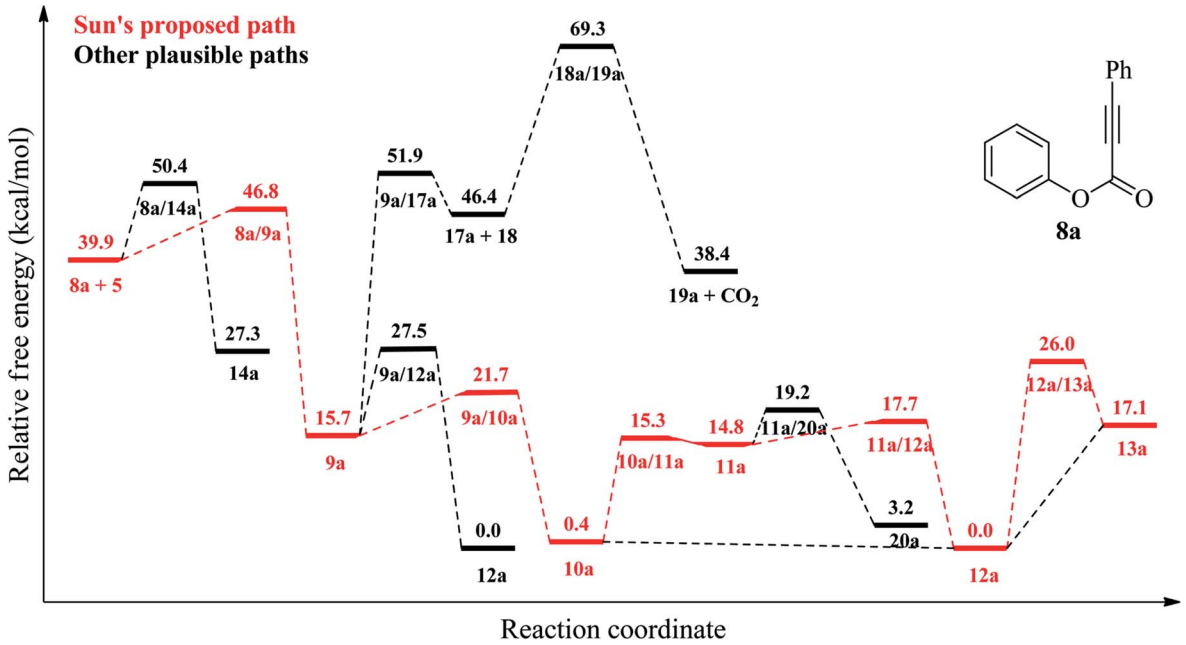
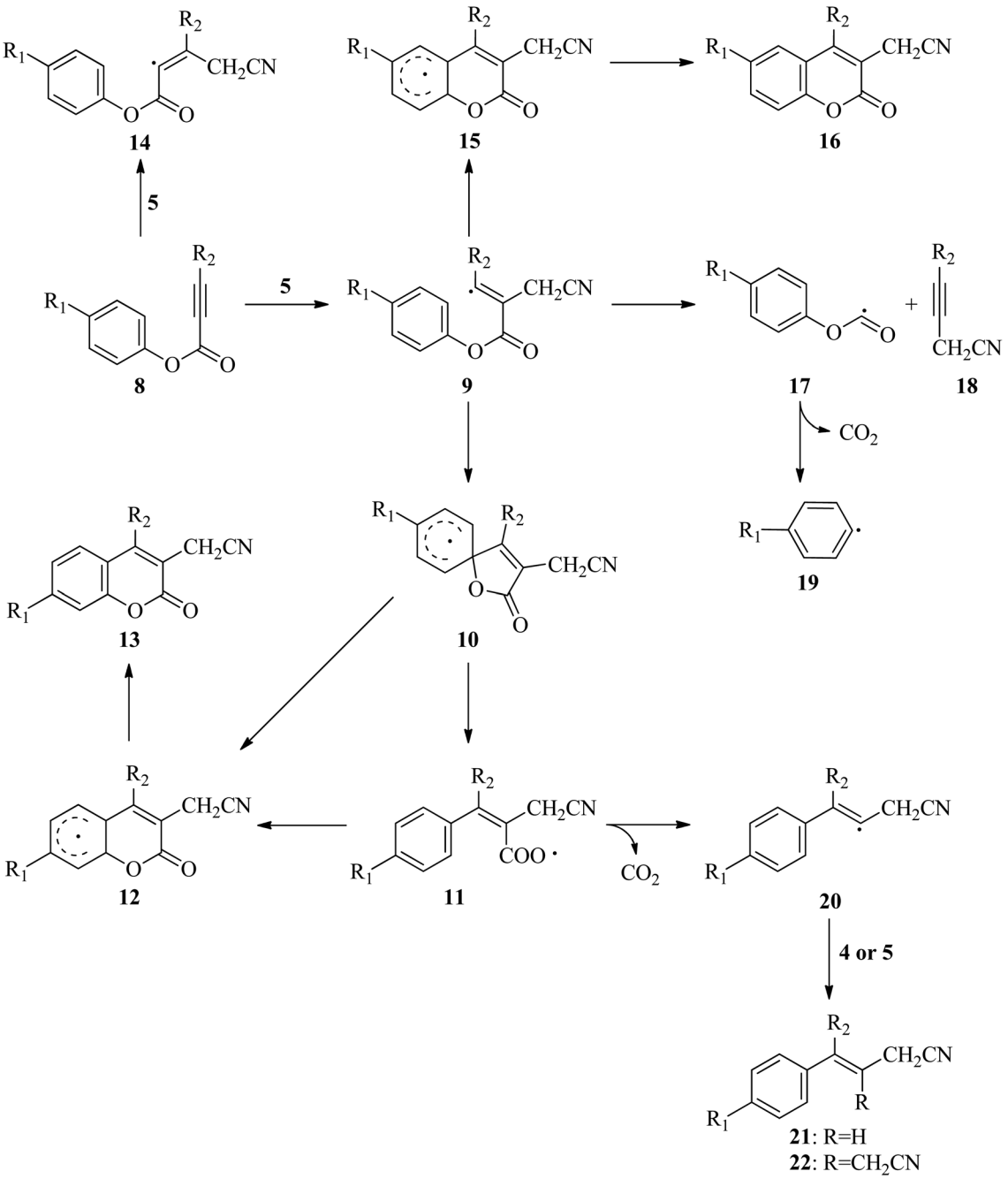


Fig. 2 Relative free energy profile (at 403.15 K) for reaction mechanism of **8a** shown in Schemes 1 and 2 at the DLPNO-CCSD(T)/cc-PVTZ//B3LYP-6-311G(d,p) level.

result clarifies why the electrophilic attack of cyanomethyl radical (**5**) to alkynes, **8**, is formed the formation of the intermediates **9**. The intramolecular spirocyclization of the alkenyl radical **9** gives the spiro-radical intermediate **10**, while the intramolecular cyclization of the alkenyl radical **9** gives the intermediate **15**. For the intramolecular spirocyclization of the alkenyl radical **9**, **9a** → **10a**, the reaction free energy and barrier are −15.3 and 6.0 kcal mol^{-1}, respectively. For the intramolecular cyclization of the alkenyl radical **9**, **9a** → **12a**, the reaction free energy and barrier are −15.7 and 11.8 kcal mol^{-1}, respectively. Also, decarboxylation of the intermediate **17** forming with release acetylene derivative **18** generates phenyl radical **19**. For the formation of the intermediate **17**, **9a** → **17a**, the reaction free energy and barrier are 30.7 and 36.2 kcal mol^{-1}, respectively. For the decarboxylation of the intermediate **17**, **17a** → **19a**, the reaction free energy and barrier are −8.0 and 22.9 kcal mol^{-1}, respectively. While the aryl migration *via* cleavage of C–O bond yields the carboxyl radical **11**, the ester migration process without the formation of the carboxyl radical **11** affords the intermediate **12**. For 1,2-aryl migration, **10a** → **11a**, the reaction free energy and barrier are 14.4 and 14.9 kcal mol^{-1}, respectively. For the **10a** → **12a** conversion, the reaction energy is −0.4 kcal mol^{-1} and 1,2-ester migration proceeds barrierless. The cyclization of carboxyl radical **11** yields the intermediate **12** oxidized by abstraction of a hydrogen radical to yield the desire product, coumarin derivatives **13**. For the cyclization of carboxyl radical **11**, **11a** → **12a**, the reaction free energy and barrier are −14.8 and 2.9 kcal mol^{-1}, respectively. For the oxidation by generating a hydrogen radical of the intermediate **12**, the reaction free energy and barrier are 17.1 and 26.0 kcal mol^{-1}, respectively. However, the oxidation of the intermediate **12** with single electron oxidation followed by deprotonation, or abstraction of the hydrogen atom by benzoyloxy radical (**2**) or *t*-butoxy radical (**3**) proceeds barrierless. The decarboxylation with release of carbon dioxide of the carboxyl radical **11** yields alkenyl radical **20**, which is ready to afford the formation of styrene derivatives **21** and **22**. For the decarboxylation of the carboxyl radical **11**, **11a** → **20a**, the reaction free energy and barrier are −11.6 and 4.4 kcal mol^{-1}, respectively.

Conclusion

In this study, all plausible mechanism for metal-free cyanomethylation of aryl alkynoates with acetonitrile has been investigated with high-level coupled-cluster methods, such as DLPNO-CCSD(T), along with the cc-pVTZ basis set. According to our computations, the decomposition of TBPB, which is the initial step of the radicalic reaction, include the highest reaction energy step and show that the rate-determining step is the formation of the benzoyloxy (**2**) and *tert*-butoxy radical (**3**) for the reaction scheme. 1,2-Ester migration in the spiro-radical intermediate **10** does not proceed *via* the formation of the carboxyl radical **11** suggested by Sun and co-workers because the relative energy of carboxyl radical **11** is nearly same that of TS **10**/**11** and activation free energy for the **11a** → **20a** conversion is very low for the proposed reaction condition. Also, solvent corrected free energies demonstrated that carboxyl radical **11** is not formed in the reaction conditions (see ESI†). Additionally, no observed styrene derivatives support that the intermediates **11** are not formed during the reaction. Our results demonstrate that the reaction of aryl alkynoates using acetonitrile as the cyanomethyl source in the presence of TBPB tends to yield the kinetically favoured product. Our results also



Scheme 2 Plausible mechanism for aryl alkanoates with cyanomethyl radical.

indicate that *t*-butoxy radical (**3**) is substantially responsible in the formation of cyanomethyl radical (**5**). The computations are compatible with experimental results. Moreover, our computations provide useful insight into the reaction mechanism of aryl alkynotes with a variety of radicals.

Computational methods

Geometry optimizations and harmonic vibrational frequency computations for the structures considered were carried out with the density functional theory (DFT), the B3LYP functional.[50–53] For this purpose, a Pople-type polarized triple-ζ split-valence basis sets, 6-311G(d,p), was used.[54–56] Single point energies were computed at the optimized geometries with the coupled-cluster singles and doubles with perturbative triples method employing the domain based local pair natural orbitals approach [DLPNO-CCSD(T)].[57,58] In DLPNO-CCSD(T) computations Dunning's correlation consistent triple-ζ split valence basis set, cc-pVTZ, is employed.[59,60] DFT computations were carried out by using the Gaussian 09 program,[61] while the ORCA package[62,63] is employed for DLPNO-CCSD(T) computations. The solvation effects were considered employing the polarizable

continuum model (PCM) in acetonitrile.[64] For the transition state (TS) between species A and B, the A/B notation is used throughout the article.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by Hakkari University, Scientific Research Project Coordination Unit (BAP; Grant no. FM21AYP1).

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