Heterogeneous photocatalytic cyanomethylarylation of alkenes with acetonitrile: synthesis of diverse nitrogenous heterocyclic compounds

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Full Research Paper

Abstract

A visible light-mediated heterogeneous photocatalytic cyanomethylarylation of alkenes with acetonitrile has been established using K-modified carbon nitride (CN-K) as a recyclable semiconductor photocatalyst. This protocol, employing readily accessible alkyl N-hydroxyphthalimide (NHPI) ester as a radical initiator, allows the efficient construction of a broad array of structural diverse nitrogenous heterocyclic compounds including indolines, oxindoles, isoquinolinones, and isoquinolinediones.

Introduction

Nitrogenous heterocyclic compounds, such as indolines [1-4], oxindoles [5-7], isoquinolinones [8-10], and isoquinolinediones [11,12], are pivotal structural motifs in numerous pharmaceuticals, agrochemicals, and bioactive natural products. The oxidative cyanomethylarylation of N-aryl/benzoyl acrylamide or allylamine involving the key C–H functionalization of readily available acetonitrile is a straightforward and powerful method to access these useful structures [13-17]. Over the last decade, although numerous protocols have been disclosed for the direct cyanomethylarylation of alkenes, most of them rely on the use of transition metals (such as catalytic amounts of Pd, Cu, Fe catalyst or stoichiometric amounts of Ag, Mn salts) and strong oxidants (including PhI(OH)₂, DTBP, and t-BuONO) in the presence of various base additives under high reaction temperatures or microwave stimulations [18-26]. Recently, visible light photoredox catalysis has emerged as a powerful and environment-friendly method in organic synthesis by activating organic molecules under mild reaction conditions [27,28]. In this context, the Li and Cai groups independently disclosed a photocatalytic cyanomethylarylation of N-aryl/benzoyl acrylamide for the synthesis of oxindoles and isoquinolinediones using diazonium salts and PIFA/1,3,5-trimethoxybenzene as radical ini-
Scheme 1: CN-K-Catalyzed cyanomethylarylation of alkenes to access diverse heterocyclic compounds.

**Results and Discussion**

Our initial investigation focused on the CN-K photocatalyzed cascade alkyl radical addition/cyclization reaction of the N-arylallylamine 1a with tert-butyl N-hydroxyphthalimide (NHPI) ester (2a), a classical alkyl radical precursor [57-59], to construct indoline product 4. Surprisingly, the solvent acetonitrile incorporated indoline 3a was observed as the major product (21%, Table 1, entry 1). Stimulated by this result, we questioned whether it would be possible to develop a general and efficient CN-K-based heterogeneous protocol for the cyanomethylarylation of N-arylallylamines with acetonitrile. Pleasingly, after the systematic evaluation of various NHPI esters, which are easily prepared from readily available carboxylic acids, the yield of the product 3a could be increased to 75% when using the primary NHPI ester 2d as a radical initiator. The concentration of the reactant had a significant effect on the reaction. When the reaction was performed under higher concentrations (0.05 M), the target product was obtained in...
Table 1: Optimization of the reaction conditions and control experiments.

| entry | PC | NHPI ester 2 | yield (%)b |
|-------|----|--------------|------------|
| 1     | CN-K | 2a | 21         |
| 2     | CN-K | 2b | 13         |
| 3     | CN-K | 2c | 49         |
| 4     | CN-K | 2d | 75 (72)c  |
| 5d    | g-C₃N₄ | 2d | 62         |
| 6     | g-C₃N₄ | 2d | 23         |
| 7     | eosin Y | 2d | 20         |
| 8     | 4CzIPN | 2d | 18         |
| 9e    | [Ru(bpy)₃]Cl₂ | 2d | 73         |
| 10e   | fac–Ir(ppy)₃ | 2d | 60         |
| 11    | CN-K | –  | 0          |
| 12    | –    | 2d | 0          |
| 13f   | CN-K | 2d | 0          |
| 14g   | CN-K | 2d | 0          |

aReaction conditions: 1a (0.1 mmol, 1 equiv), 2 (0.2 mmol, 2 equiv), CH₃CN (6 mL), PC (1 mg/mL), 2 × 24 W blue LEDs (460 ± 5 nm) without extra heating (at 40–45 °C) for 72 h. bDetermined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. cData in parentheses are the isolated yields. dPerformed with 0.05 M of 1a for 120 h. eUsing 2 mol % of PC. fIn the dark. gUnder air.

62% yield after prolonged reaction time (Table 1, entry 5). Traditional g-C₃N₄ exhibited a low catalytic activity for this transformation (Table 1, entry 6). Switching from CN-K to a homogeneous organo photocatalyst such as eosin Y and 4CzIPN, led to lower yields of the desired product (Table 1, entries 7 and 8). The expensive Ru/Ir-based metal complexes gave similar results for the transformation (Table 1, entries 9 and 10). In the control experiments, no reaction was observed in the absence of the NHPI ester, CN-K, or light, which unambiguously manifested all of them were requisite for this transformation (Table 1, entries 11–13). In addition, no desired product was detected under air, further indicating a radical-initiated process was involved in the reaction (Table 1, entry 14).

Under the optimal reaction conditions, we first evaluated the scope of N-arylallylamines for the synthesis of indolines. As shown in Scheme 2, substrates with various electron-donating groups (such as methyl or methoxy) and electron-withdrawing groups (chloro, bromo, or cyano) at the para-position of the aryl ring smoothly reacted with acetonitrile to afford the 5-substituted cyanomethylated indolines 3a–f in good yields (67–75%). When the benzene ring of the substrates was changed to naphthalene, the reaction successfully provided the benzoindoline 3g in 56% yield. Substrates with an N-Boc group also worked well to deliver the corresponding indoline 3h in 77% yield. Moreover, a scale-up reaction of 1a (2 mmol) was conducted, affording the corresponding product 3a (0.28 g) in a yield of 62%.

Next, we examined the efficiency of the CN-K-catalyzed cyanomethylarylation of N-benzoylallylamines for the synthesis of isoquinolinone derivatives. Under similar reaction conditions, various N-benzoylallylamines bearing either electron-donating or withdrawing substituents in the para-position of the phenyl ring (Scheme 3) were smoothly converted to the corresponding isoquinoliones 6a–e in moderate to good yields (51–69%, Scheme 3). The regioselectivity of this reaction was studied using the meta-substituted substrate 5f. The results indi-
Scheme 2: CN-K-catalyzed cyanomethylarylation of \( N \)-arylallylamines for the synthesis of indolines. Reaction conditions: 1 (0.2 mmol, 1 equiv), 2d (0.4 mmol, 2 equiv), CH\(_3\)CN (8 mL), CN-K (1 mg/mL), 2 × 24 W blue LEDs (460 ± 5 nm) without extra heating (at 40–45 °C). \(^{a}\)Performed with 0.017 M of 1.

Scheme 3: CN-K-catalyzed cyanomethylarylation of \( N \)-benzoylallylamines for the synthesis of isoquinolinones. Reaction conditions: 5 (0.2 mmol, 1 equiv), 2d (0.6 mmol, 3 equiv), CH\(_3\)CN (8 mL), CN-K (1 mg/mL), 2 × 24 W blue LEDs (460 ± 5 nm), 60 °C.

| Product | Yield | Regioisomer | Note |
|---------|-------|-------------|------|
| 3a      | 72%   | Ac          | 62% (2 mmol scale) |
| 3b      | 72%   | Ac          |
| 3c      | 67%   | Ac          |
| 3d      | 74%   | Ac          |
| 3e      | 73%   | Ac          |
| 3f      | 75%   | Ac          |
| 3g      | 56%\(^{a}\) | Ac          |
| 3h      | 77%\(^{a}\) | Boc        |

The established CN-K-catalyzed cyanomethylarylation protocol is not only effective for the above unactivated alkenes. Also activated alkenes including \( N \)-aryl and \( N \)-benzoyl acrylamides...
can be employed as substrates, allowing for the construction of valuable oxindole and isoquinolininedione derivatives. With respect to the generality of the \( \text{N-aryl acrylamides} \) (Scheme 4), a range of frequently encountered functional groups were well tolerated affording the methoxy (8b), methyl (8c), the halogenated (8d–f), trifluoromethyl (8g), cyano (8h), and carbonyl (8i and 8j) substituted products with 70–82% yield, which provide opportunities for further modification. The \textit{ortho}-substituted substrate 7k gave the corresponding product 8k in a comparable yield (69%). Also the substrate bearing a \textit{meta}-substituent exhibited good reactivity, delivering the corresponding regioisomers 8l and 8l' in 62% with 1:1.6 ratio. Moreover, the naphthalene and tetrahydroisoquinoline-derived acrylamides were also compatible, giving the polycyclic products 8m and 8n in 77% and 70%, respectively. Additionally, protecting groups such as isopropyl, benzyl, or phenyl on the nitrogen atom did not considerably affect the yield (8o–8q, 68–76%). Substrates with benzyl and phenyl groups at the \( \alpha \)-position afforded the products 8r and 8s in 74% and 24%, respectively. Substrates with a phenyl group at the \( \beta \)-position underwent arylation with the opposite regioselectivity to afford the six-membered product 8t in 22% yield. Regarding the scope of \( \text{N-benzoyl acrylamides} \), the electronic property of a substituent on the phenyl ring also had little influence on the reaction, furnishing the desired isoquinolininediones 10a–c in moderate to high yields (Scheme 5, 60–70%).

To illustrate the practicability of this CN-K-based heterogeneous photocatalysis protocol, a recycling procedure was established. The CN-K was recovered via simple centrifugation after the reaction and subsequently reused. As shown in Figure 1, the CN-K catalyst could be recycled at least five times without the loss of photocatalytic activity when applied in the cyanomethylarylation of \( \text{N-arylallylamine} \) 1a with acetonitrile.

We also utilized this strategy to test \( n \)-butyl nitrile under the standard conditions. As shown in Scheme 6a, the corresponding oxindole 11 was obtained in 45% yield. The synthetic utility

\[ \text{Ar} \quad \text{N} \quad \text{O} \quad \text{R}^1 + \text{CH}_{3}\text{CN} \quad \text{CN-K (0.5 mg/mL)} \quad \text{blue LEDs (460 nm)} \quad \text{NHPI ester 2d (2 equiv)} \quad c = 0.025 \text{ M, 80 °C} \]

\[ \text{Ar} \quad \text{N} \quad \text{O} \quad \text{R}^1 \quad \text{CN} \]

\[ \text{8a, R = H, 70%} \]
\[ \text{8b, R = OMe, 73%} \]
\[ \text{8c, R = Me, 76%} \]
\[ \text{8d, R = F, 82%} \]
\[ \text{8e, R = Cl, 74%} \]

\[ \text{8f, R = Br, 76%} \]
\[ \text{8g, R = CF}_3, \text{ 73%} \]
\[ \text{8h, R = CN, 79%}\text{,}^a \]
\[ \text{8i, R = CO}_2\text{Me, 74%} \]
\[ \text{8j, R = Ac, 73%}\text{,}^a \]

\[ \text{8l, 62% (1:1.6)} \]
\[ \text{8m, 77%} \]
\[ \text{8n, 70%} \]

\[ \text{8r, 74%}\text{,}^b \]
\[ \text{8s, 24%}\text{,}^b \]
\[ \text{8t, 22% (5.3:1)}\text{,}^b,^c \]

\[ \text{8o, R = iPr, 76%}\text{,}^b \]
\[ \text{8p, R = Bn, 72%}\text{,}^b \]
\[ \text{8q, R = Ph, 68%}\text{,}^b \]

\textbf{Scheme 4:} CN-K-catalyzed cyanomethylarlylation of \( \text{N-aryl acrylamides} \) for the synthesis of oxindoles. Reaction conditions: 7 (0.2 mmol, 1 equiv), 2d (0.4 mmol, 2 equiv), \( \text{CH}_3\text{CN (8 mL)} \), CN-K (0.5 mg/mL), 2 × 24 W blue LEDs (460 ± 5 nm), 80 °C. \(^a\text{Conducted at 100 °C.} \)

\(^b\text{Performed with 1 mg/mL of CN-K.}\)

\(^c\text{Ratio = trans/cis.}\)
Scheme 5: CN-K-catalyzed cyanomethylation of \(N\)-benzoyl acrylamides for the synthesis of isoquinolinediones. Reaction conditions: \(9\) (0.2 mmol, 1 equiv), \(2d\) (0.4 mmol, 2 equiv), CH\(_3\)CN (8 mL), CN-K (1 mg/mL), 2 × 24 W blue LEDs (460 ± 5 nm), 80 °C.

Figure 1: Evaluation of catalyst recycling. Reaction conditions: \(1a\) (0.1 mmol, 1 equiv), \(2d\) (0.2 mmol, 2 equiv), CH\(_3\)CN (6 mL), CN-K (1 mg/mL), 2 × 24 W blue LEDs (460 ± 5 nm) without extra heating (at 40–45 °C). After each reaction, the catalyst was recovered by centrifugation and reused in the next cycle.

was further demonstrated by a series of successful derivatizations of the cyano-substituted oxindole \(8a\). For instance, after the Ritter reaction, \(8a\) was smoothly converted to \(N\)-tert-butylation acetamide \(12\) in 96% yield (Scheme 6b). A modified Witte–Seeliger reaction led to the formation of oxazoline \(13\) in 41% yield (Scheme 6c). Furthermore, the tricyclic indoline \(14\), a structural motif in diverse natural products [4], could be obtained in 60% yield through a reductive cyclization reaction (Scheme 6d).

To investigate the mechanism of the cyanomethylationation of alkenes, a series of control experiments was performed (Scheme 7). The cyanomethylationation reaction of \(7a\) gave the desired compound \(8a\) as the major product in 70% yield, along
Scheme 6: Further survey of reaction scope and derivatization studies of 8a.

(a) 7a + n-BuCN, CN-K (1 mg/mL), blue LEDs (460 nm) → 11, 45%, 1:1 dr

(b) 8a, t-BuOAc, excess H2SO4, 70 °C, 3 h → 12, 96%

(c) 8a, NiH2CH2CH2OH, Cd(OAc)2·2H2O (20 mol %), PhMe, 130 °C, 36 h → 13, 41%

(d) 8a, LiAlH4 (2 equiv), THF, rt, 3 h → 14, 60%

with 23% yield of the byproduct 15. The latter compound was generated through a cascade alkyl radical addition/cyclization of the NHPI ester 2d to N-aryl acrylamide 7a (Scheme 7a). When the reaction was conducted in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO), both the desired product 8a and the byproduct 15 were not observed, which indicated that the reaction proceeds through a radical pathway (Scheme 7b). It is worth mentioning that when 7a was submitted to the reaction in a 1:1 mixture of CH3CN/CD3CN as the solvent, the product 8a was furnished in 44% yield and the corresponding deuterated product was not observed (Scheme 7c). In addition, when 7a was reacted in CD3CN, only the byproduct 15 was obtained in 34% yield (Scheme 7d). These results indicate a large primary isotope effect, which suggest that the C(sp3)–H bond cleavage of acetonitrile contributed to the rate-determining step.

Based on the present results and the literature [18-26,31,60], the reaction pathway is proposed as shown in Scheme 8. As reported in our previous work [32], CN-K has a band gap of 2.72 eV with a conduction band potential of −1.88 V vs SCE, which is thermodynamically favored to induce a single-electron reduction of the NHPI ester (<−1.28 V vs SCE in CH3CN) [61] to generate the corresponding alkyl radical A. The subsequent hydrogen abstraction by radical A yields the key alkyl radical B. The addition of radical B or A to the alkene 7a following by an intramolecular cyclization provides the radical intermediates C or E, which are oxidized by the hole of CN-K via SET delivering the product 8a or byproduct 15 after deprotonation.

Conclusion
We have demonstrated the application of a heterogeneous CN-K semiconducting photocatalyst in the cyanomethylarylation of alkenes with acetonitrile utilizing a readily available NHPI ester as radical initiator. This transition metal-free protocol tolerates a broad range of both unactivated and activated alkenes including N-aryl/benzoylallylamines and acrylamides, providing a facile access to a series of structural diverse indoline, oxindole, isoquinolinone, and isoquinolinedione derivatives with high efficiency. The CN-K catalyst can be easily recovered from the reaction mixture and reused several times, illustrating the practicability of this heterogeneous photocataly-
Scheme 7: Experiments for the mechanistic study.

Scheme 8: Plausible mechanism of the CN-K-catalyzed cyanomethylation of alkenes.
sis protocol. Further applying this sustainable and environmentally friendly CN-K heterogeneous photocatalyst to realize other synthetic useful transformations is undergoing.

Supporting Information

Supporting Information File 1
Full experimental details, compound characterisation, and copies of NMR spectra.

References

1. Newhouse, T.; Baran, P. S. J. Am. Chem. Soc. 2008, 130, 10886–10887. doi:10.1021/ja0842307
2. Mohn, T.; Piltzko, I.; Hamburger, M. Phytochemistry 2009, 70, 924–934. doi:10.1016/j.phytochem.2009.04.019
3. Zhang, D.; Song, H.; Qin, Y. Acc. Chem. Res. 2011, 44, 447–457. doi:10.1021/ar20004w
4. Matsuura, T.; Overman, L. E.; Poon, D. J. J. Am. Chem. Soc. 1998, 120, 6500–6503. doi:10.1021/ja980778x
5. Marti, C.; Carreira, E. M. Eur. J. Org. Chem. 2003, 2209–2219. doi:10.1002/ejoc.200300050
6. Jiang, T.; Kuhn, K. L.; Wolff, K.; Yin, H.; Bleza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewska, D.; He, Y. Bioorg. Med. Chem. Lett. 2006, 16, 2109–2112. doi:10.1016/j.bmcl.2006.01.066
7. Singh, G. S.; Desta, Z. Y. Chem. Rev. 2012, 112, 6104–6155. doi:10.1021/cr300135y
8. Scott, J. D.; Williams, R. M. Chem. Rev. 2002, 102, 1669–1730. doi:10.1021/cr010212u
9. Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saia, E. J. Med. Chem. 2014, 57, 1299–1322. doi:10.1021/jm401509e
10. Hekal, M. H.; Abu El-Azm, F. S. M.; Sallam, H. A. J. Heterocycl. Chem. 2019, 56, 795–803. doi:10.1002/jhet.3448
11. Billamboz, M.; Bailly, F.; Barreca, M. L.; De Luca, L.; Mouscadet, J.-F.; Calmels, C.; Andréola, M.-L.; Wittrouv, M.; Christ, F.; Debyser, Z.; Cotelle, P. J. Med. Chem. 2008, 51, 7717–7730. doi:10.1021/jm8007085
12. Billamboz, M.; Bailly, F.; Lion, C.; Touati, N.; Vezin, H.; Calmels, C.; Andreola, M.-L.; Christ, F.; Debyser, Z.; Cotelle, P. J. Med. Chem. 2011, 54, 1812–1824. doi:10.1021/jm1014692
13. Girard, S. A.; Knauber, T.; Li, C.-J. Angew. Chem., Int. Ed. 2014, 53, 74–100. doi:10.1002/anie.201304268
14. López, R.; Palomo, C. Angew. Chem., Int. Ed. 2015, 54, 13170–13184. doi:10.1002/anie.201502493
15. Song, R.-J.; Liu, Y.; Xie, Y.-X.; Li, J.-H. Synthesis 2015, 47, 1195–1209. doi:10.1055/s-0034-1379903
16. Li, C.-C.; Yang, S.-D. Org. Biomol. Chem. 2016, 14, 4365–4377. doi:10.1039/c6ob00554c
17. Chu, X.-Q.; Ge, D.; Shen, Z.-L.; Loh, T.-P. ACS Catal. 2018, 8, 258–271. doi:10.1021/acscatal.7b03334
18. Wu, T.; Mu, X.; Liu, G. Angew. Chem., Int. Ed. 2011, 50, 12578–12581. doi:10.1002/anie.201104575
19. Li, J.; Wang, Z.; Wu, N.; Gao, G.; You, J. Chem. Commun. 2014, 50, 15049–15051. doi:10.1039/c4cc07667b
20. Pan, C.; Zhang, H.; Zhu, C. Org. Biomol. Chem. 2015, 13, 361–364. doi:10.1039/c4ob02172j
21. Li, X.; Xu, J.; Gao, Y.; Fang, H.; Tang, G.; Zhao, Y. J. Org. Chem. 2015, 80, 2621–2626. doi:10.1021/acs.joc.5b01777
22. Tang, S.; Li, S.-H.; Li, Z.-H.; Zhou, D.; Sheng, R.-L. Tetrahedron Lett. 2015, 56, 1423–1426. doi:10.1016/j.tetlet.2015.01.175
23. Ni, Z.; Huang, X.; Wang, J.; Pan, Y. RSC Adv. 2016, 6, 522–526. doi:10.1039/c5ra23471a
24. Liang, D.; Song, X.; Xu, L.; Sun, Y.; Dong, Y.; Wang, B.; Li, W. Tetrahedron 2019, 75, 3459–3503. doi:10.1016/j.tet.2019.05.018
25. Pan, C.; Wang, Y.; Wu, C.; Yu, J.-T. Catal. Commun. 2019, 131, 105802. doi:10.1016/j.catcom.2019.105802
26. Zhang, H.; Chen, P.; Liu, G. Synlett 2012, 23, 2749–2752. doi:10.1055/s-0032-1316555
27. Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Chem. Soc. Rev. 2016, 45, 2044–2056. doi:10.1039/c5cs00655d
28. Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Angew. Chem., Int. Ed. 2018, 57, 10034–10072. doi:10.1002/anie.201709766
29. Lu, Y.; Zhang, J.-L.; Song, R.-J.; Li, J.-H. Org. Chem. Front. 2014, 1, 1289–1294. doi:10.1039/c4qo00251b
30. Zhang, J.-L.; Liu, Y.; Song, R.-J.; Jiang, G.-F.; Li, J.-H. Synlett 2014, 25, 1031–1035. doi:10.1055/s-0033-1340956
31. Lu, M.; Zhang, T.; Tan, D.; Chen, C.; Zhang, Y.; Huang, M.; Cai, S. Adv. Synth. Catal. 2019, 361, 4237–4242. doi:10.1002/adsc.201900712
32. Yang, Q.; Pan, G.; Wei, J.; Wang, W.; Tang, Y.; Cai, Y. ACS Sustainable Chem. Eng. 2021, 9, 2367–2377. doi:10.1021/acssuschemeng.0c08771
33. Liu, X.; Fechner, N.; Antonietti, M. Chem. Soc. Rev. 2013, 42, 8237–8265. doi:10.1039/c3cs60195e
34. Wu, M.; Yan, J.-M.; Tang, X.-n.; Zhao, M.; Jiang, Q. ChemSusChem 2014, 7, 2654–2658. doi:10.1002/cssc.2014022180
35. Zhang, G.; Lin, L.; Li, G.; Zhang, Y.; Savateev, A.; Zafeiratos, S.; Wang, X.; Antonietti, M. Angew. Chem., Int. Ed. 2018, 57, 9372–9376. doi:10.1002/anie.201804702
36. Xu, Y.; He, X.; Zhong, H.; Singh, D. J.; Zhang, L.; Wang, R. Appl. Catal., B 2019, 246, 349–355. doi:10.1016/j.apcatb.2019.01.069
37. Lang, X.; Chen, X.; Zhao, J. Chem. Soc. Rev. 2014, 43, 473–486. doi:10.1039/c3cs60188a
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