Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2024, **34**, 673–675

Mendeleev Communications

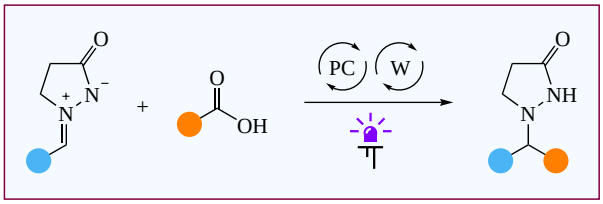
Visible light-driven decarboxylative alkylation of azomethine imines with carboxylic acids

Zakhar M. Rubanov, Mikhail D. Kosobokov, Vitalij V. Levin and Alexander D. Dilman*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: dilman@ioc.ac.ru

DOI: 10.1016/j.mencom.2024.09.015

The alkylation of cyclic five-membered azomethine imines with carboxylic acids proceeds under irradiation with 400 nm light using a dual catalytic system consisting of 9-arylacridine and tetrabutylammonium decatungstate. Azomethine imines containing aromatic, heterocyclic and aliphatic groups are suitable for the process providing pyrazolidin-3-ones in 42–98% yields.



Keywords: azomethine imines, carboxylic acids, radical reactions, photocatalysis, acridine catalysis, decatungstate, pyrazolidin-3-ones.

Pyrazolone is a common five-membered heterocyclic motif present in the structures of a number of commercial drugs and prospective bioactive compounds.[1–9] Drugs of the phenylbutazone family are used for animal treatment by virtue of their anti-inflammatory properties[1,2] (Figure 1). For the 1,2-diarylpyrazolidin-3-one derivatives, a wide range of antibacterial activity was recently reported.[3] Edaravone, a neuroprotective agent with antioxidant properties,[4] and the pyrazolone based experimental HIV drug[5] also exemplify the importance of compounds of this class. The promising fungicides for plant protection have recently been found among pyrazolones.[9]

Cyclic azomethine imines bearing pyrazolidinone moiety **1** have long been recognized as versatile starting materials for the introduction of the dinitrogen cycle due to their availability and diverse reactivity.[10] Azomethine imines **1** can be easily synthesized from the corresponding aldehydes, acrylates, and hydrazine. Various [3 + *n*] cycloadditions resulting in N–N fused bicyclic systems[11–16] and nucleophilic additions at the iminium carbon[17–19] are well established reactions of azomethines. Open-shell reactivity of azomethine imines has not attracted significant attention until mild radical generation based on photoredox catalysis was recently developed.[20–25] Several studies on radical addition to azomethine imines **1** using the visible light-driven methodology were carried out[26] (Scheme 1, part A). Thus, the Hantzsch esters were used as sources of radicals of various types.[27–29] Amines,[30,31] fluorinated alkyl bromides,[32] and *N*-sulfonyl cyclopropylamines,[33] were also employed as precursors of radical species. Generation of radicals under electrochemical conditions from *N*-hydroxyphthalimide esters was described as well.[34]

Carboxylic acids are versatile feedstock compounds in organic chemistry[35,36] often used as substrates for radical reactions. Among various methodologies developed for decarboxylative radical generation,[37,38] acridine photocatalysis has outstanding advantages as it utilizes free acids at room

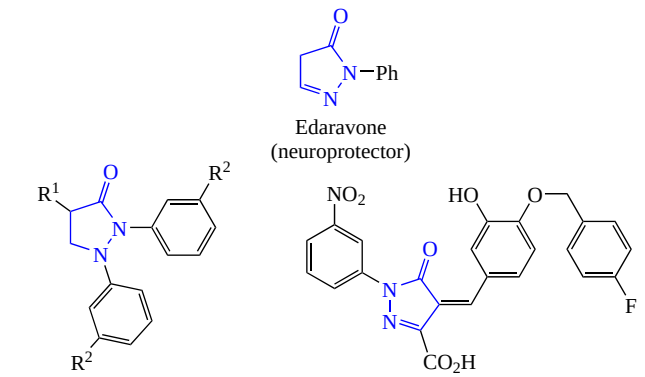
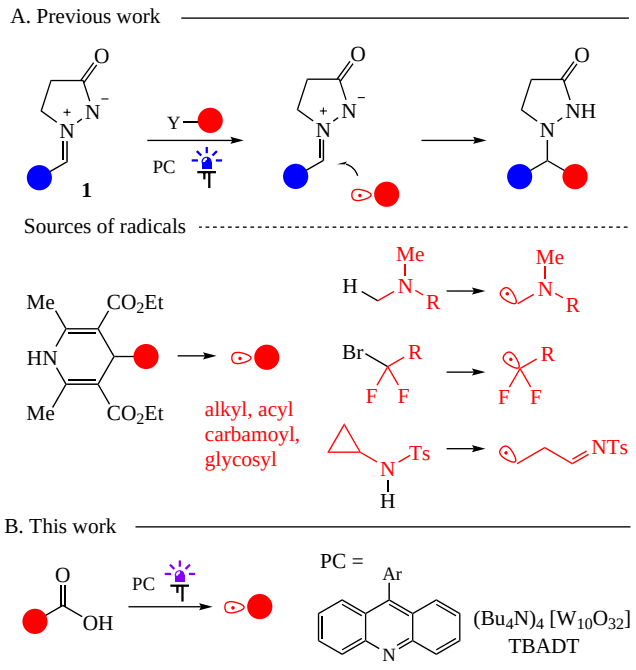


Figure 1 Bioactive substances containing pyrazolone motif.

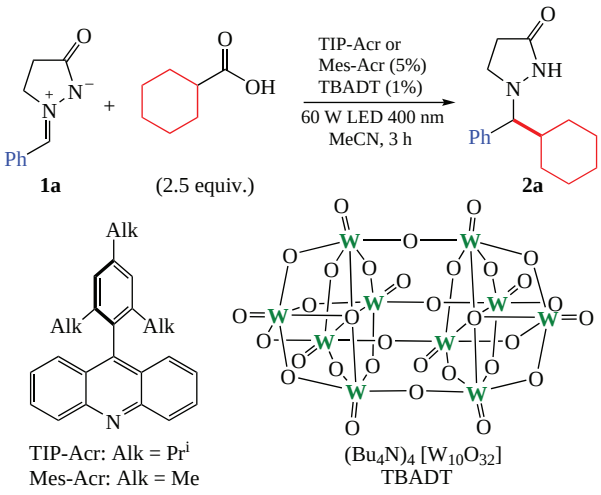


Scheme 1

temperature with no need for auxiliaries, metals, or strong bases. The ability of acridines to activate carboxylic acids under visible irradiation was noticed in the late 1960s.[39] However, the intensive development of this field began only in the 2020s by the Larionov group,[40–47] along with our research group[48–51] and others.[52–54]

Recently, we introduced a novel photocatalytic method using a combination of acridine and tetrabutylammonium decatungstate (TBADT) photocatalysts for the addition of carboxylic acids to imines and hydrazones.[55] In this dual catalytic system, the decatungstate facilitates the turnover of the acridine photocatalyst through the hydrogen atom transfer. Inspired by this phenomenon, here we expand the acridine/decatungstate protocol to cyclic azomethine imines (see Scheme 1, part B). After brief optimization, we found that azomethine imine **1a** efficiently reacted with cyclohexanecarboxylic acid in the presence of bulky acridine catalyst TIP-Acr and TBADT to afford pyrazolidinone product **2a** (Scheme 2, Table 1, entry 1). The reaction proceeded at room temperature under violet light irradiation (400 nm) in acetonitrile. Without TBADT, the yield was significantly lower (entry 2), and in the absence of acridine, no product was detected (entry 4). Less hindered 9-mesitylacridine catalyst showed comparable results in optimization (entry 5) but exhibited poor reproductivity with other substrates. The reaction conducted under 450 nm irradiation also provided product **2a** in good yield (entry 6).

Primary, secondary, and tertiary radicals generated from the corresponding acids R^2CO_2H were successfully attached to azomethine imines **1a–f** under the optimal conditions (Scheme 3). For the primary phenethyl radical, product **2c** was obtained in moderate yield. On the other hand, stabilized methoxymethyl radicals generated from methoxyacetic acid led to pyrazolidin-3-one **2d** in excellent yield. The reaction tolerated heterocycles (products **2e–g**) and a halogen substituent (**2f**). The aromatic substituent in reactant **1** was not necessary

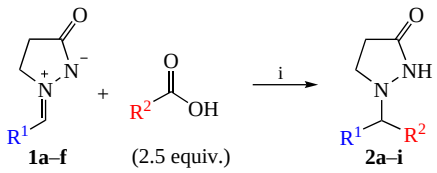


Scheme 2

Table 1 Optimization studies for conversion of azomethine imine **1a** into pyrazolidinone **2a** (see Scheme 2).

Entry	Reaction conditions	Yield of **2a** (%)[a]
1	Optimal[b]	83 (78[c])
2	Without TBADT	61
3	In CH_2Cl_2 without TBADT	48
4	Without TIP-Acr	–
5	With Mes-Acr instead of TIP-Acr	82
6	With 450 nm LED	83

[a] Determined by NMR using CH_2Br_2 as internal standard. [b] Optimal conditions: TIP-Acr (5 mol%), TBADT (1 mol%), 60 W LED 400 nm, MeCN, 20 °C, 3 h. [c] Isolated yield.



a R^1 = Ph
b R^1 = 2-thienyl
c R^1 = 5-bromo-2-thienyl
d R^1 = 2-pyridyl
e R^1 = *n*-C_7H_{15}
f R^1 = Bu^t

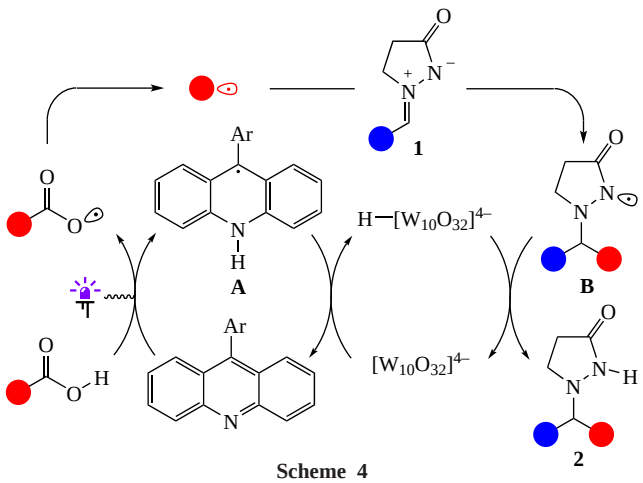
a R^1 = Ph, R^2 = Cy, 78%
b R^1 = Ph, R^2 = Bu^t, 79%
c R^1 = Ph, R^2 = $Ph(CH_2)_2$, 42%
d R^1 = Ph, R^2 = $MeOCH_2$, 98%
e R^1 = 2-thienyl, R^2 = Cy, 65%
f R^1 = 5-bromo-2-thienyl, R^2 = Cy, 87%
g R^1 = 2-pyridyl, R^2 = Cy, 56%
h R^1 = *n*-C_7H_{15}, R^2 = Cy, 81%
i R^1 = Bu^t, R^2 = Cy, 66%

Scheme 3 *Reagents and conditions*: i, 0.5 mmol of **1a–f**, TIP-Acr (5 mol%), TBADT (1 mol%), 60 W 400 nm LED, MeCN, 20 °C, 3 h. For **2c**, 10 mol% of TIP-Acr was used. Additional experiment for **2a**: 5 mmol scale, 80 W 400 nm LED, 74% yield (0.957 g).

for the reaction, as *n*-heptyl- or *tert*-butyl-containing azomethine imines **1e**,**f** gave the desired products **2h**,**i** in good yields. While the reactions were typically performed on 0.5 mmol of azomethine imines, they can also be conducted in a 5 mmol scale of **1a** using slightly higher irradiation power (80 W) without significant loss of yield, as was demonstrated for the synthesis of product **2a**. Unfortunately, the reactions with azomethine imine derived from 5-hydroxymethylfurfural failed and led to complex mixtures.

The proposed reaction mechanism is shown in Scheme 4. First, carboxylic acid is activated with photoexcited acridine to generate carboxylic radical which would expel carbon dioxide. The activation of carboxylic acid proceeds as proton coupled electron transfer and is accompanied by the formation of acridinium radical **A** having the N–H bond. Addition of the alkyl radical at the C=N bond of azomethine imine **1** leads to formation of N-centered radical **B**. Proposedly, the hydrogen atom transfer between **B** and acridinum intermediate **A** is inefficient. It is believed that this step is promoted by decatungstate,[56,57] so the decatungstate may abstract the hydrogen atom from **A** followed by transferring it to radical **B** with the regeneration of the acridine photocatalyst and formation of product **2**. It is likely that decatungstate anion works as a hydrogen atom transfer agent in the ground state, as blue $H–[W_{10}O_{32}]^{4–}$ particles were observed under low-energy 450 nm light irradiation, whereas the decatungstate anion $[W_{10}O_{32}]^{4–}$ itself has no absorption in the visible region (see Table 1, entry 6).[56]

In summary, a photocatalytic method for the synthesis of 1-derivatized pyrazolidin-3-ones by reaction of azomethine



Scheme 4

imines with carboxylic acids has been developed. The reaction features the combined use of 9-aryl-substituted acridine and tetrabutylammonium decatungstate which are needed for the radical generation and photocatalyst recycling, respectively.

This work was supported by the Russian Science Foundation (grant no. 21-73-10129).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.09.015.

References

1 V. S. Moses and A. L. Bertone, *Vet. Clin. Equine Pract.*, 2002, **18**, 21.
2 N. Y. Shpigel, M. Winkler, A. Saran and G. Zrv, *J. Vet. Med. A*, 1996, **43**, 331.
3 S. A. Mokbel, R. K. Fathalla, L. Y. El-Sharkawy, A. H. Abadi, M. Engel and M. Abdel-Halim, *Bioorg. Chem.*, 2020, **99**, 103759.
4 C. Bailly, P.-E. Hecquet, M. Kouach, X. Thuru and J.-F. Goossens, *Bioorg. Med. Chem.*, 2020, **28**, 115463.
5 T. Yousfi, A. Elliott, M. Hanane, R. Merdes and A. Moyano, *Molecules*, 2016, **21**, 1655.
6 M. J. Ahsan, A. Ali, A. Ali, A. Thiriveedhi, M. A. Bakht, M. Yusuf, Salahuddin, O. Afzal and A. S. A. Altamimi, *ACS Omega*, 2022, **7**, 38207.
7 M. Asif, M. Imran and A. Husain, *J. Chil. Chem. Soc.*, 2021, **66**, 5149.
8 L. M. Blair and J. Sperry, *J. Nat. Prod.*, 2013, **76**, 794.
9 A. S. Budnikov, E. R. Lopat'eva, I. B. Krylov, O. O. Segida, A. V. Lastovko, A. I. Ilovaisky, G. I. Nikishin, A. P. Glinushkin and A. O. Terent'ev, *J. Agric. Food Chem.*, 2022, **70**, 4572.
10 A. Deepthi, N. V. Thomas and S. L. Sruthi, *New J. Chem.*, 2021, **45**, 8847.
11 U. Grošelj, F. Požgan, B. Štefane and J. Svete, *Synthesis*, 2018, **50**, 4501.
12 C. Nájera, J. M. Sansano and M. Yus, *Org. Biomol. Chem.*, 2015, **13**, 8596.
13 M. Wang, Z. Huang, J. Xu and Y. R. Chi, *J. Am. Chem. Soc.*, 2014, **136**, 1214.
14 G. Qiu, Y. Kuang and J. Wu, *Adv. Synth. Catal.*, 2014, **356**, 3483.
15 R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, III, H. Guo and O. Kwon, *J. Am. Chem. Soc.*, 2011, **133**, 13337.
16 A. Suárez, C. W. Downey and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 11244.
17 H.-Y. Wang, C.-W. Zheng, Z. Chai, J.-X. Zhang and G. Zhao, *Nat. Commun.*, 2016, **7**, 12720.
18 R. Shintani, Y.-T. Soh and T. Hayashi, *Org. Lett.*, 2010, **12**, 4106.
19 H. Kawai, A. Kusuda, S. Nakamura, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2009, **48**, 6324.
20 L. Candish, K. D. Collins, G. C. Cook, J. J. Douglas, A. Gómez-Suárez, A. Jolit and S. Keess, *Chem. Rev.*, 2022, **122**, 2907.
21 R. Cannalire, S. Pelliccia, L. Sancineto, E. Novellino, G. C. Tron and M. Giustiniano, *Chem. Soc. Rev.*, 2021, **50**, 766.
22 S. Crespi and M. Fagnoni, *Chem. Rev.*, 2020, **120**, 9790.
23 F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer and F. Glorius, *Chem. Soc. Rev.*, 2018, **47**, 7190.
24 N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075.
25 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322.
26 S. Oudeyer, V. Levacher, H. Beucher and J.-F. Brière, *Molecules*, 2023, **28**, 1071.
27 J. Li, J. Phetcharawetch, M. Qi, S. H. Kyne, C. Kuhakarn, B. Zhong and P. W. H. Chan, *New J. Chem.*, 2023, **47**, 19421.
28 B. T. Matsuo, P. H. R. Oliveira, J. T. M. Correia and M. W. Paixão, *Org. Lett.*, 2021, **23**, 6775.
29 R. O. Gonçalves, P. H. R. Oliveira, I. S. de Jesus, N. P. Debia, D. S. Lüdtke and M. W. Paixão, *Org. Biomol. Chem.*, 2023, **21**, 5516.
30 B. T. Matsuo, J. T. M. Correia and M. W. Paixão, *Org. Lett.*, 2020, **22**, 7891.
31 J. Li, L. Carli, S. H. Kyne and P. W. H. Chan, *Adv. Synth. Catal.*, 2023, **365**, 2422.
32 P.-J. Xia, Z.-P. Ye, D. Song, J.-W. Ren, H.-W. Wu, J.-A. Xiao, H.-Y. Xiang, X.-Q. Chen and H. Yang, *Chem. Commun.*, 2019, **55**, 2712.
33 J. Qiu, W. Li, X. Li, Y. Cao, C.-X. Pan and H. Li, *Org. Lett.*, 2023, **25**, 8000.
34 L. Leleu, T. Martzel, A. Fall, M. Sanselme, V. Levacher, S. Oudeyer and J. F. Briere, *Chem. Commun.*, 2022, **58**, 6100.
35 J. Iglesias, I. Martínez-Salazar, P. Maireles-Torres, D. M. Alonso, R. Mariscal and M. López Granados, *Chem. Soc. Rev.*, 2020, **49**, 5704.
36 Q. Wu, X. Bao, W. Guo, B. Wang, Y. Li, H. Luo, H. Wang and N. Ren, *Biotechnol. Adv.*, 2019, **37**, 599.
37 S. Karmakar, A. Silamkoti, N. A. Meanwell, A. Mathur and A. K. Gupta, *Adv. Synth. Catal.*, 2021, **363**, 3693.
38 J. Xuan, Z.-G. Zhang and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2015, **54**, 15632.
39 R. Noyori, M. Katô, M. Kawanisi and H. Nozaki, *Tetrahedron*, 1969, **25**, 1125.
40 H. T. Dang, G. C. Haug, V. T. Nguyen, N. T. H. Vuong, V. D. Nguyen, H. D. Arman and O. V. Larionov, *ACS Catal.*, 2020, **10**, 11448.
41 V. T. Nguyen, V. D. Nguyen, G. C. Haug, N. T. H. Vuong, H. T. Dang, H. D. Arman and O. V. Larionov, *Angew. Chem., Int. Ed.*, 2020, **59**, 7921.
42 V. T. Nguyen, G. C. Haug, V. D. Nguyen, N. T. H. Vuong, H. D. Arman and O. V. Larionov, *Chem. Sci.*, 2021, **12**, 6429.
43 V. D. Nguyen, G. C. Haug, S. G. Greco, R. Trevino, G. B. Karki, H. D. Arman and O. V. Larionov, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210525.
44 V. D. Nguyen, R. Trevino, S. G. Greco, H. D. Arman and O. V. Larionov, *ACS Catalysis*, 2022, **12**, 8729.
45 V. T. Nguyen, G. C. Haug, V. D. Nguyen, N. T. H. Vuong, G. B. Karki, H. D. Arman and O. V. Larionov, *Chem. Sci.*, 2022, **13**, 4170.
46 H. T. Dang, V. D. Nguyen, G. C. Haug, H. D. Arman and O. V. Larionov, *JACS Au*, 2023, **3**, 813.
47 K. Zhuang, G. C. Haug, Y. Wang, S. Yin, H. Sun, S. Huang, R. Trevino, K. Shen, Y. Sun, C. Huang, B. Qin, Y. Liu, M. Cheng, O. V. Larionov and S. Jin, *J. Am. Chem. Soc.*, 2024, **146**, 8508.
48 D. L. Lipilin, M. O. Zubkov, M. D. Kosobokov and A. D. Dilman, *Chem. Sci.*, 2024, **15**, 644.
49 M. O. Zubkov, M. D. Kosobokov, V. V. Levin and A. D. Dilman, *Org. Lett.*, 2022, **24**, 2354.
50 K. A. Zhilyaev, D. L. Lipilin, M. D. Kosobokov, A. I. Samigullina and A. D. Dilman, *Adv. Synth. Catal.*, 2022, **364**, 3295.
51 I. A. Dmitriev, V. V. Levin and A. D. Dilman, *Org. Lett.*, 2021, **23**, 8973.
52 J. G. L. de Araujo, M. d. S. B. da Silva, J. C. C. V. Bento, A. M. de Azevêdo, A. M. de M. Araújo, A. S. D. dos Anjos, C. A. Martínez-Huitle, E. V. dos Santos, A. D. Gondim and L. N. Cavalcanti, *Chem. – Eur. J.*, 2023, **29**, e202302330.
53 J. A. Andrews, J. Kalepu, C. F. Palmer, D. L. Poole, K. E. Christensen and M. C. Willis, *J. Am. Chem. Soc.*, 2023, **145**, 21623.
54 A. Adili, A. B. Korpusik, D. Seidel and B. S. Sumerlin, *Angew. Chem., Int. Ed.*, 2022, **61**, e202209085.
55 Z. M. Rubanov, V. V. Levin and A. D. Dilman, *Org. Lett.*, 2024, **26**, 3174.
56 D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa and I. Ryu, *ACS Catal.*, 2018, **8**, 701.
57 P. P. Singh, S. Sinha, P. Gahtori, S. Tivari and V. Srivastava, *Org. Biomol. Chem.*, 2024, **22**, 2523.

Received: 7th May 2024; Com. 24/7493