EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202400281

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Direct Introduction of an Acetyl Group at the α-Carbon Atom of an Arene Ring through an Amide Photo-Fries Rearrangement upon Exposure to UV Light

Myeonggeuk Kim[+],[a] Ha-Na Na[+],[a, d] Liu-lan Shen,*[c, d] and Jin Hyun Jeong*[a, b]

We employed an amide photo-Fries rearrangement for the synthesis benzoheterocyclic compounds and found that direct acylation of the α-carbon atom in an arene ring can occur upon exposure to ultraviolet (UV) light. In this reaction, the *N*-acetyl group of amides underwent rearrangement to the α-position across the bridgehead carbon atom under UV–C light. The reaction conditions were gentle and safe. Moreover, this reaction proves to be more convenient for selectively manipulating benzoheterocyclic compounds in comparison to traditional approaches involving Lewis acid catalysts or anionic reagents.

Introduction

Benzoheterocyclic structures can be found in numerous drugs of both natural and synthetic origin,[1] and active pharmaceutical ingredients, such as caboxamycin, rufloxacin, antipathine A, flumequine, boxazomycin B, azilsartan, and candesartan (Figure 2). It remains unsolved to introduce one more carbon chain to the hetero-derived arene ring, even though these kinds of motif are commonly used in pharmaceuticals (Figure 2). To solve this problem, a Fries rearrangement used to directly introduce a carbon chain into the hetero-derived arene ring (Figure 1).

The Fries rearrangement is a reaction in which phenolic esters can be converted to hydroxyaryl ketones by heating under acidic conditions, such as hydrofluoric acid (HF),[2] aluminum chloride ($AlCl_3$),[2] boron trifluoride (BF_3),[2–3] titanium(IV) chloride ($TiCl_4$),[4] or tin(IV) chloride ($SnCl_4$).[4] Initially discovered by Anderson and Reese,[5] the cation-induced photo-

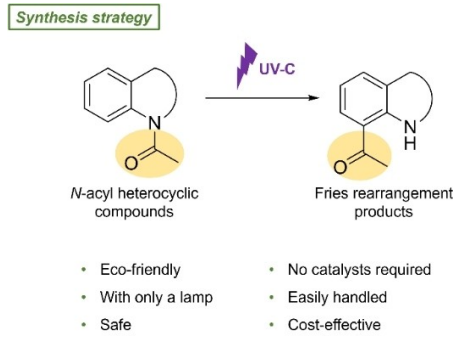


Figure 1. Synthesis strategy of this study.

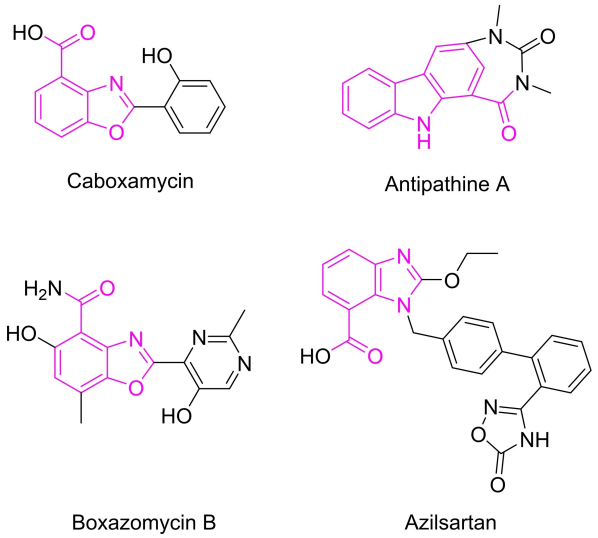


Figure 2. Examples of drugs containing acetyl groups.

Fries rearrangement has been further explored in subsequent studies on the photo-Fries rearrangement.[6] Photo-Fries rearrangement is similar to Fries rearrangement, which is catalyzed by classical Lewis acids,[7] but the former relies on a radical/light-induced reaction mechanism facilitated by a photochem-

[a] *M. Kim,[+] H.-N. Na,[+] Prof. Dr. J. H. Jeong*
College of Pharmacy, Yonsei Institute of Pharmaceutical Sciences
Yonsei University
85 Songdogwahak-ro, Yeonsu-gu, Incheon, 21983, Republic of Korea
E-mail: organicjeong@snu.ac.kr
organicjeong@gmail.com

[b] *Prof. Dr. J. H. Jeong*
WHO GBC Education Center
Seoul National University
82 Baegot 2-ro, Siheung-si, Gyeonggi-do, 15011, Republic of Korea

[c] *Dr. L.-l. Shen*
College of Pharmacy
Yonsei University
85 Songdogwahak-ro, Yeonsu-gu, Incheon, 21983, Republic of Korea
E-mail: liulanx@smartbiopharm.co.kr

[d] *H.-N. Na,[+] Dr. L.-l. Shen*
SmartBioPharm Co., Ltd.
No. 313, Pilot Plant, Incheon Technopark, 12 Gaetbeol-ro, Yeongsu-gu, Incheon, 21999, Republic of Korea

[+] *These authors contributed equally to this work.*

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202400281

ical process (Figure 3 and 4). The radical mechanisms of the photo-Fries rearrangement predominantly manifest in singlet excited states.[6a,b,8]

The amide photo-Fries rearrangement of the *N*-acetyl group on the aromatic ring has been a subject of long-standing research. Instances of this reaction include the creation of micelles through the photo-Fries rearrangement of a surfactant,[9] as well as the production of an enantiomeric quinazoline derivative through a photo-Fries rearrangement utilizing naturally occurring amino acids.[10] Previous studies have demonstrated that the direct acetylation at the α-position past the adjacent bridgehead carbon of a benzoheterocyclic compound requires a complex synthetic approach, which may involve prolonged reflux,[11] the use of palladium catalytic media,[11a,12] or the application of the microwave[13] condition.

Herein, a novel approach is presented for the direct acylation of a benzoheterocyclic compound through amide photo Fries rearrangement. We devised a gentle and uncomplicated amide photo-Fries rearrangement to form acylated benzoheterocyclic compounds in which the amide moiety is wrapped juxtaposed with an arene ring.

Results and Discussion

Previous studies have shown the feasibility of Fries rearrangements in benzoheterocyclic compounds by crossing the bridgehead carbon to the α-position. Examples are cationic photo-Fries rearrangements and anionic Fries rearrangements using non-nucleophilic reagents, such as lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidylamide (LTPA).[14] However, both types of Fries rearrangements resulted in low yield and conversion rates because they were also rearranged to positions other than the α-position past the adjacent bridgehead carbon.[14]

The conventional cationic photo-Fries rearrangement is a harsh reaction conducted under harsh conditions in UV–C with a power of 100 W or more.[8c,e,15] We used the identical UV–C but with lower watts potential light source (80 W) and proceeded the rearrangement reaction to get the acylated α-carbon which cross past the adjacent bridgehead carbon.

First, acetylation was conducted on the general type of each structure to use benzoheterocyclic compound with *N*-acetyl

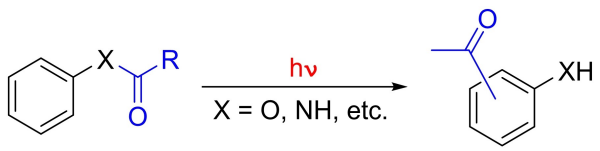


Figure 3. Fundamental concept of the photo-Fries rearrangement.

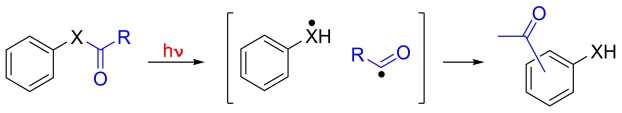


Figure 4. Radical mechanism of photo-Fries rearrangement.

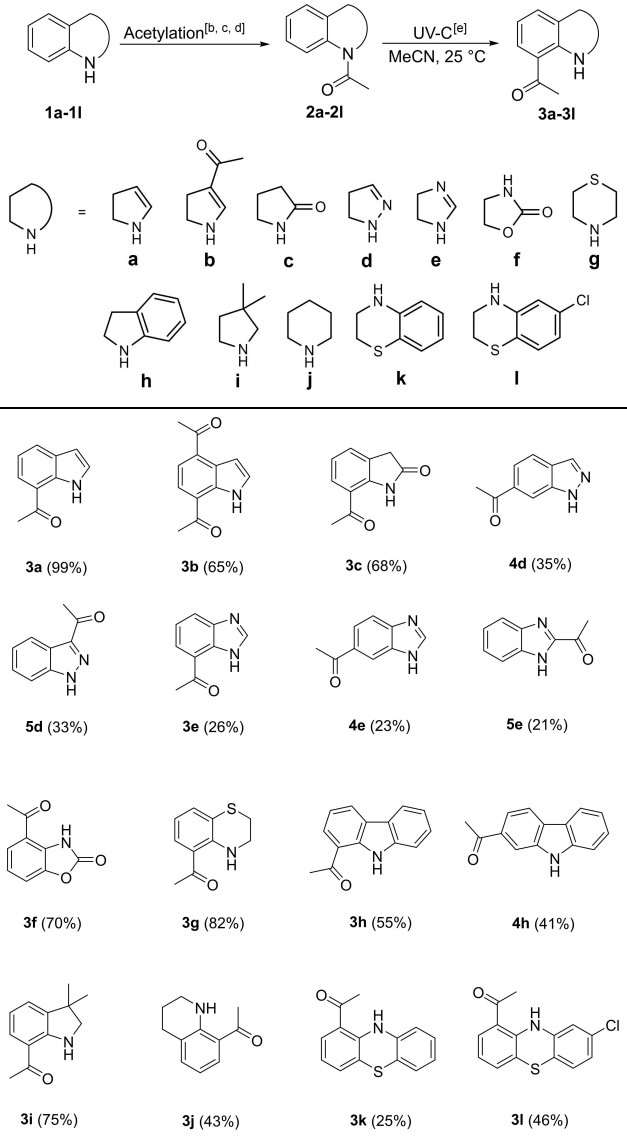
group in Table S1. In order to determine suitable wavelength bands for synthesis, we conducted a condition optimization search in the darkroom, blue LED (465 nm), visible light (380–780 nm), UV–A (352 nm), UV–B (306 nm), and UV–C (253.7 nm). Then, in the dark room without light exposure, the photo-Fries rearrangement did not occur. The photo-Fries rearrangement did not proceed even in light sources with longer wavelengths such as blue LEDs and visible light. In the UV region, the reaction yield was high in the order of C > B > A, which was the shorter wavelength. UV–A enabled the reaction to synthesize **3a** (Table S2, entry 1) in only **2a**, an indole derivative in a low yield, whereas other compounds (**3b** to **3l**) remained unconverted. UV–B led to a rearrangement, but it was not the regioselectivity we wanted (Table S2). Most of the starting materials remained unconverted as well. In contrast, UV–C was mostly rearranged to the α-position past the adjacent bridgehead carbon we wanted, and the starting material was also completely consumed (Table S2). Through the optimization process, we continued our experiments using UV–C range of the spectrum (Table 1).

As a result, indole derivative **3a** could be obtained in a remarkable yield of 99%, and **3b** (65%) and **3c** (68%) could also be obtained with yields exceeding 50%. The indazole derivatives were rearranged to two positions. Two compounds were obtained in comparable amounts: **5d** (33%) rearranged to position 3 (the amines in the ring were numbered in the counterclockwise direction) and **4d** (35%) rearranged to position 7. Benzimidazole derivatives were rearranged to three distinct positions: **5e** (21%) rearranged to position 2, and **3e** (26%) rearranged to position 8, and **4e** (23%), position 7 adjacent to it. Benzoxazole derivative **3f** was obtained in a yield of 70%. Benzothiazine derivative **3g** (82%) was obtained with high efficiency. Carbazole derivatives **3h** (55%) and **4h** (41%) were rearranged to two positions, with a preference for position 12 in **3h**. The yield of dimethylindole derivative of **3i** was 75%, a tetrahydroquinoline derivative **3j** reached 43%, the phenothiazine derivatives **3k** (25%) and **3l** (46%), respectively. Additionally, we used ammonium persulfate as a radical initiator under UV light, but there was no significant rate-escalating effect (Table 2). Our reaction proceeded at room temperature, and ammonium persulfate did not significantly function as a radical initiator. As indicated by the Table 2's results, rearrangement occurred even under UV irradiation without ammonium persulfate. The reaction, when influenced by UV light, transitions through a planar six-membered ring cyclic transition state. During this process, the energy level of the transition state is influenced by the degree of planarity and aromaticity. Compounds **2i** and **2j** exhibit somewhat poor planarity, making it challenging to form a flat six-membered ring, while compound **2l** displays relatively low aromaticity. Consequently, if a radical is generated by UV light and a six-membered ring does not immediately form, or if the radical is generated by persulfate, it is likely to dissociate quickly without undergoing a rearrangement reaction.

Based on these results, we supposed a radical mechanism based on a traditional rearrangement mode (Figure 5). The acyl group of amides on benzoheterocyclic compounds will form a

Research Article
doi.org/10.1002/ejoc.202400281

Table 1. Scope of photo-Fries rearrangement past the adjacent bridgehead carbon atom.[a]



[a] Yields of products refer to isolated material after purification. [b] **1** (1 equiv.), triethylamine (3 equiv.), acetic anhydride (4 equiv.), 4-dimethylaminopyridine (0.38 equiv.), 1,2-dichloroethane, room temperature, 24 h. [c] **1** (1 equiv.), triethylamine (2.5 equiv.), acetyl chloride (2 equiv.), dichloromethane, room temperature, 2 h. [d] **1** (1 equiv.), acetyl chloride (2 equiv.), toluene, 50 °C, 1 h. [e] 80 W UV–C mercury lamp (λ_{max} = 253.7 nm); MeCN: acetonitrile; UV: ultraviolet.

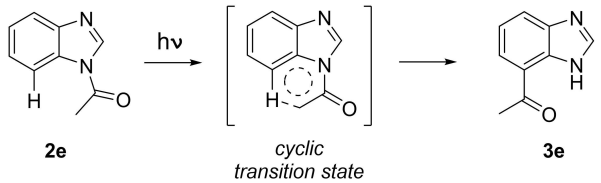


Figure 5. The anticipated mechanism for photo-Fries rearrangement using UV–C.

stable six-membered-ring transition state and activate under UV–C light conditions to form an acyl radical, which rearranges to the α-carbon atom on the neighboring arene ring.

Conclusions

We studied amide photo-Fries rearrangement using ultraviolet light, in which *N*-acetyl groups directly cross the adjacent bridgehead carbon atom to the α-position for a novel synthetic approach to modifying benzoheterocyclic compound structures. In this study, we validated that the acyl group of amides on a polycyclic ring can be rearranged directly to the α-carbon atom of an adjacent arene ring.

This amide photo-Fries rearrangement enables Fries rearrangement to be regioselective in benzoheterocyclic compounds. This could contribute to simple, inexpensive, safe, and eco-friendly synthetic methods in the fields of organic synthesis,

Table 2. Optimization of the reaction conditions with radical initiator.[a]

Entry	Compd.	Prod.	Yield[b] [%]			
			Ammonium persulfate (1 equiv.)	*t* [h]	No ammonium persulfate	*t* [h]
1	**2a**	**3a**	98	40	99	40
2	**2b**	**3b**	50	60	65	60
3	**2c**	**3c**	60	60	68	60
4	**2d**	**4d**	30	60	35	60
5	**2d**	**5d**	33	60	33	60
6	**2e**	**3e**	24	16	26	16
7	**2e**	**4e**	23	16	23	16
8	**2e**	**5e**	20	16	21	16
9	**2f**	**3f**	55	16	70	16
10	**2g**	**3g**	74	24	82	24
11	**2h**	**3h**	48	16	55	16
12	**2h**	**4h**	35	16	41	16
13	**2i**	**3i**	0	16	75	16
14	**2j**	**3j**	0	60	43	40
15	**2k**	**3k**	21	60	25	40
16	**2l**	**3l**	0	40	46	40

[a] **2** (50 mg), acetonitrile (5 mL), 80 W UV–C mercury lamp (λ_{max} = 253.7 nm), room temperature. [b] Yields of products refer to isolated material after purification; Compd.: compound; Prod.: product; UV: ultraviolet.

the pharmaceutical industry, and biochemistry (Figure 1). As a follow-up study, we plan to use the reaction in a continuous flow system, in the hope of achieving less space, less labor, less cost, and enhancing overall yield.

Experimental Section

General procedure for photo-Fries rearrangement under UV–C: All photoreactions were performed in quartz test tubes until the starting material disappeared under an 80 W UV–C mercury lamp (λ_{max} = 253.7 nm) at room temperature on a scale of 300 μmol. After completion of the reaction, the reaction mixture was quenched using saturated sodium bicarbonate (1×20 mL), and the resulting mixture was extracted with dichloromethane (1×20 mL). Then, the product was washed with water (1×20 mL). The organic layer was dried using magnesium sulfate and filtered. The organic layer was then concentrated using a rotary evaporator. The residue was purified by flash column.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: heterocycles · photochemistry · radical reactions · rearrangement · regioselectivity

[1] a) A. Caruso, A. Barbarossa, A. Carocci, G. Salzano, M. S. Sinicropi, C. Saturnino, *Appl. Sci.* **2021**, *11*, 6192; b) E. Kabir, M. Uzzaman, *Results Chem.* **2022**, *4*, 100606.
[2] M. B. Hocking, *J. Chem. Technol. Biotechnol.* **1980**, *30*, 626–641.
[3] J. L. Boyer, J. E. Krum, M. C. Myers, A. N. Fazal, C. T. Wigal, *J. Org. Chem.* **2000**, *65*, 4712–4714.
[4] R. Martin, *Org. Prep. Proced. Int.* **1992**, *24*, 369–435.
[5] J. C. Anderson, C. B. Reese, *J. Chem. Soc. (Resumed)* **1963**, *0*, 1781–1784.
[6] a) J. W. Meyer, G. S. Hammond, *J. Am. Chem. Soc.* **1972**, *94*, 2219–2228; b) L. K. Crevatín, S. M. Bonesi, R. Erra-Balsells, *Helv. Chim. Acta* **2006**, *89*, 1147–1157; c) M. S. Kharasch, G. Stampa, W. Nudenberg, *Science* **1952**, *116*, 309–309; d) G. Guerrini, M. Taddei, F. Ponticelli, *J. Org. Chem.* **2011**, *76*, 7597–7601.
[7] a) K. Fries, W. Pfaffendorf, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 212–219; b) K. Fries, G. Finck, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 4271–4284; c) J. March, *Advanced Organic Chemistry*, 3 ed., John Wiley & Sons **1985**; d) A. H. Blatt, *Organic Reactions, Vol. 1*, John Wiley & Sons **1942**.
[8] a) W. Gu, R. G. Weiss, *J. Photochem. Photobiol. C* **2001**, *2*, 117–137; b) N. P. Gritsan, Y. P. Tsentalovich, A. V. Yurkovskaya, R. Z. Sagdeev, *J. Phys. Chem.* **1996**, *100*, 4448–4458; c) C. E. Kalmus, D. M. Hercules, *J. Am. Chem. Soc.* **1974**, *96*, 449–456; d) S. M. Bonesi, L. K. Crevatín, R. Erra-Balsells, *Photochem. Photobiol. Sci.* **2004**, *3*, 381–388; e) S. M. Bonesi, R. Erra-Balsells, *J. Photochem. Photobiol. A* **1997**, *110*, 271–284.
[9] D. Iguchi, R. Erra-Balsells, S. M. Bonesi, *Photochem. Photobiol. Sci.* **2016**, *15*, 105–116.
[10] C.-C. Chien, S.-C. Kao, C.-J. Chen, Y.-K. Wu, *Chem. Commun.* **2020**, *56*, 15470–15472.
[11] a) W.-L. Jia, N. Westerveld, K. M. Wong, T. Morsch, M. Hakkennes, K. Naksomboon, M. Á. Fernández-Ibáñez, *Org. Lett.* **2019**, *21*, 9339–9342; b) D. A. Scott, L. A. Dakin, D. J. Del Valle, R. Bruce Diebold, L. Drew, T. W. Gero, C. A. Ogoe, C. A. Omer, G. Repik, K. Thakur, Q. Ye, X. Zheng, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1382–1384.
[12] G. Xie, Y. Zhao, C. Cai, G.-J. Deng, H. Gong, *Org. Lett.* **2021**, *23*, 410–415.
[13] G. Brusotti, J. Habermann, O. Azzolina, S. Collina, *Lett. Org. Chem.* **2006**, *3*, 943–947.

[14] a) A. Hallberg, A. Svensson, A. R. Martin, *Tetrahedron Lett.* **1986**, *27*, 1959–1962; b) J. C. Riggs, K. J. Singh, M. Yun, D. B. Collum, *J. Am. Chem. Soc.* **2008**, *130*, 13709–13717; c) K. J. Singh, D. B. Collum, *J. Am. Chem. Soc.* **2006**, *128*, 13753–13760.

[15] a) N. Kawatsuki, T. Neko, M. Kurita, A. Nishiyama, M. Kondo, *Macromolecules* **2011**, *44*, 5736–5742; b) I. F. Molokov, Y. P. Tsentalovich, A. V. Yurkovskaya, R. Z. Sagdeev, *J. Photochem. Photobiol. A* **1997**, *110*, 159–165; c) R. A. Finnegan, J. J. Mattice, *Tetrahedron* **1965**, *21*, 1015–1026; d) R. A. Finnegan, D. Knutson, *Tetrahedron Lett.* **1968**, *9*, 3429–3432; e) Y. Katsuhara, H. Maruyama, Y. Shigemitsu, Y. Odaira, *Tetrahedron Lett.* **1973**, *14*, 1323–1326; f) C. Cui, X. Wang, R. G. Weiss, *J. Org. Chem.* **1996**, *61*, 1962–1974.

[16] I. Medina-Mercado, E. O. Asomoza-Solís, E. Martínez-González, V. M. Ugalde-Saldívar, L. G. Ledesma-Olvera, J. E. Barquera-Lozada, V. Gómez-Vidales, J. Barroso-Flores, B. A. Frontana-Uribe, S. Porcel, *Chem. Eur. J.* **2020**, *26*, 634–642.

[17] S. Auvin, P.-E. C. D. Lassauniere, US 7384933B2, **2008**, p. 12.

Manuscript received: March 28, 2024
Revised manuscript received: April 14, 2024
Accepted manuscript online: April 15, 2024
Version of record online: May 17, 2024