Tetrahedron Letters 55 (2014) 3146–3148

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

2-Chloroanthraquinone-catalyzed aerobic photo-oxidative synthesis of diacylamines from benzylamides

Izuho Itoh [a], Yoko Matsusaki [a], Akitoshi Fujiya [a], Norihiro Tada [a], Tsuyoshi Miura [b], Akichika Itoh [a,*]

[a] *Gifu Pharmaceutical University, 1-25-4, Daigaku-nishi, Gifu 501-1196, Japan*
[b] *Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

ARTICLE INFO

Article history:
Received 27 January 2014
Revised 24 March 2014
Accepted 28 March 2014
Available online 4 April 2014

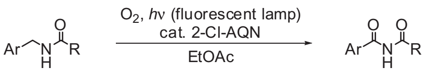
Keywords:
Aerobic
Anthraquinone
Diacylamine
Photo-oxidation
Visible light

ABSTRACT

In this Letter, we report the aerobic photo-oxidative synthesis of diacylamines from benzylamides in the presence of molecular oxygen and catalytic amounts of 2-chloroanthraquinones under visible light irradiation from a fluorescent lamp.

Diacylamines are important structural motifs as starting materials for the preparation of *N*-containing heterocycles such as triazoles,[1] oxazols,[2] and imidazolins.[3] Furthermore, diacylamines have also been studied from the viewpoint of biological activity.[4] In general, the preparation of diacylamines involves the acylation of amides with carboxylic acid anhydrides,[5] acyl chlorides,[4,6] ketenes,[7] α,α,α-trichloromethyl carbonyl compounds,[8] or enol esters;[9] however, these methods suffer from various drawbacks such as low product yields, strong environmental impacts of the solvents used, or wastes produced. Other methods for the synthesis of diacylamines is oxidation of amides, which using transition metal catalysts (Ru,[10] Cr,[11] Cu,[12] Co,[13] Mn,[14] Fe,[15] Ag/Cu[16]) combined with stoichiometric reoxidants. On the other hand, metal-free oxidation of amides with stoichiometric amounts of organic reagents such as DMP,[17] *tert*-butylperoxyiodane,[18] and DDQ[19] has been reported to date. From these perspectives, we have studied oxidation processes based on the use of molecular oxygen, and have observed that benzylamides were oxidized to the corresponding diacylamines successfully under external photoirradiation in the presence of catalytic amounts of iodine[20] or HBr.[21] Although these methods are interesting from a green chemistry perspective due to the non-use of heavy metals, waste reduction, the use of molecular oxygen, the use of inexpensive reagents, and the use of environmentally low-impact solvents, the use of halogen reagents remains an obstacle to the development of a more environmentally benign method. Recently, we have studied photo-oxidative reactions with organo-photocatalysts such as anthraquinones.[22] Here we report our detailed study of the aerobic photo-oxidation of benzylamides to the corresponding diacylamines under visible-light irradiation in the presence of an organophotocatalyst (Scheme 1).

To explore this approach, we selected *N*-benzylacetamide (**1a**) as a test substrate to optimize the reaction conditions (Table 1). Among the solvents and catalysts irradiated with a fluorescent lamp under an oxygen atmosphere (entries 1–13), ethyl acetate in combination with 2-chloroanthraquinone (2-Cl-AQN) provides *N*-acetylbenzamide (**2a**) most efficiently (entry 4). Addition of base and acid resulted in a slight reduction in the yield (entries 14 and 15). Reducing of the catalyst-loading to 0.05 equiv gave lower yield of **2a** (entry 17). Furthermore, increasing of the catalyst-loading to 0.2 equiv also resulted in lower yield probably because of low solubility of 2-Cl-AQN in ethyl acetate (entry 18). Finally, prolonging the reaction time to 30 h gave the best result (entry 16). Notably, 2-Cl-AQN, visible-light irradiation, and molecular oxygen are necessary for this reaction because **2a** cannot be satisfactorily



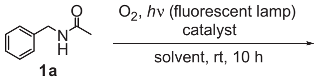
Scheme 1. Aerobic photooxidative synthesis of diacylamines.

---

* Corresponding author. Tel.: +81 58 237 3931; fax: +81 58 237 5979.
E-mail address: itoha@gifu-pu.ac.jp (A. Itoh).

http://dx.doi.org/10.1016/j.tetlet.2014.03.123
0040-4039/

Table 1
Study of reaction conditions[a]



Entry	Catalyst (equiv)	Solvent	Yield[b] (%)
1	AQN (0.1)	EtOAc	61
2	2-^{t}Bu-AQN (0.1)	EtOAc	66
3	1-Cl-AQN (0.1)	EtOAc	0
4	2-Cl-AQN (0.1)	EtOAc	88
5	AQN-2-CO$_2$H (0.1)	EtOAc	85
6	Anthracene (0.1)	EtOAc	6
7	Benzophenone (0.1)	EtOAc	2
8	Methylene blue (0.1)	EtOAc	1
9	2-Cl-AQN (0.1)	Hexane	Trace
10	2-Cl-AQN (0.1)	*i*Pr$_2$O	0
11	2-Cl-AQN (0.1)	CHCl$_3$	13
12	2-Cl-AQN (0.1)	AcOH	75
13	2-Cl-AQN (0.1)	H$_2$O	0
14	2-Cl-AQN (0.1)	EtOAc	81[c]
15	2-Cl-AQN (0.1)	EtOAc	86[d]
16	2-Cl-AQN (0.1)	EtOAc	95[e]
17	2-Cl-AQN (0.05)	EtOAc	49
18	2-Cl-AQN (0.2)	EtOAc	76
19	—	EtOAc	0
20	2-Cl-AQN (0.1)	EtOAc	0[f]
21	2-Cl-AQN (0.1)	EtOAc	26[g]
22	2-Cl-AQN (0.1)	EtOAc	73[h]

[a] Reaction conditions: **1a** (0.3 mmol) and catalyst in solvent (3 mL) were stirred and irradiated externally with a fluorescent lamp under oxygen atmosphere at room temperature for 10 h.

[b] ^{1}H NMR yields.

[c] The reaction was carried out with K$_2$CO$_3$ (0.1 equiv).

[d] The reaction was carried out with AcOH (0.1 equiv).

[e] The reaction was carried out for 30 h.

[f] The reaction was carried out in the dark.

[g] The reaction was carried out under argon.

[h] The reaction was carried out under air.

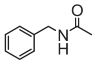
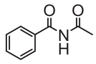
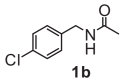
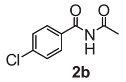
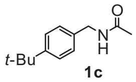
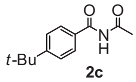
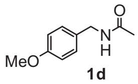
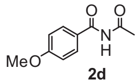
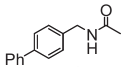
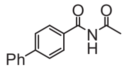
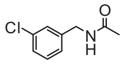
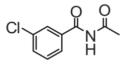
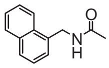
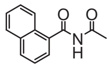
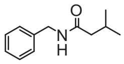
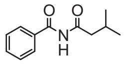
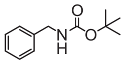
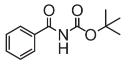
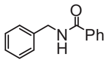
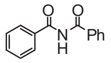
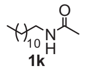
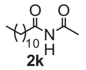
obtained without them (entries 19–21). Interestingly, this reaction proceeded in good yield, even under an air atmosphere (entry 22).

Table 2 shows the scope and limitations of this oxidation process under the aforementioned optimized reaction conditions.[23] *N*-Benzylacetamides that possess an electron donating or withdrawing group at their aromatic nucleus, produce the corresponding diacylamines in high to excellent yields (entries 1–6). *N*-(1-Naphthylmethyl)acetamide (**1g**) produced the corresponding product (**2g**) in only 30% yield (entry 7). *N*-Benzyl-3-methylbutylamide (**1h**), *N*-(phenylmethyl)-1,1-dimethylethyl ester carbamic acid (**1i**), and *N*-benzylbenzamide (**1j**) were converted into the corresponding diacylamines in good yields (entries 8–10). Unfortunately, *N*-dodecylacetamide (**1k**), an aliphatic amide, was intact under these conditions (entry 11). It should be noted that this reaction can easily be performed on a 3 mmol scale to give **2a** in 76% yield without further optimization (entry 1).

Scheme 2 shows a plausible mechanism for this oxidation. The proposed mechanism takes into account the necessity of continuous irradiation, a catalytic amount of 2-Cl-AQN, and molecular oxygen for this reaction. The amide initially reacts with AQN*, which is generated from AQN by irradiation with a fluorescent lamp,[24] to give benzyl radical species **3**. The radical species **3** trap molecular oxygen to afford peroxyradical **4**, which is subsequently transferred to hydroperoxide **5** by abstraction of a hydrogen radical from **1** or AQH. A diacylamine **2** is formed through dehydration from **5**.

Table 2
Aerobic photooxidative of diacylamines[a]

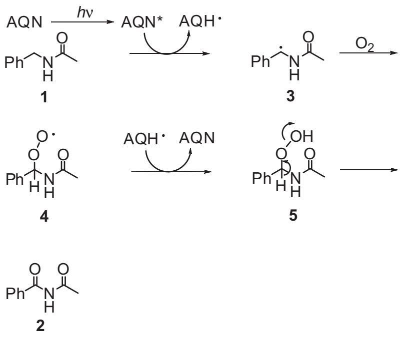
$$\text{substrate} \xrightarrow[\text{EtOAc, rt}]{\text{O}_2,\ h\nu\ \text{(fluorescent lamp)},\ \text{2-Cl-AQN (0.1 equiv)}} \text{product}$$

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	30	88 (76)[c]
2	 **1b**	 **2b**	30	93
3	 **1c**	 **2c**	20	82
4	 **1d**	 **2d**	50	83
5	 **1e**	 **2e**	20	99
6	 **1f**	 **2f**	30	81
7	 **1g**	 **2g**	30	30
8	 **1h**	 **2h**	30	80
9	 **1i**	 **2i**	30	71
10	 **1j**	 **2j**	70	74
11	 **1k**	 **2k**	70	0

[a] Reaction conditions: **1** (0.3 mmol) and 2-Cl-AQN (0.1 equiv) in ethyl acetate (3 mL) were stirred and irradiated externally with a fluorescent lamp under oxygen atmosphere at room temperature.

[b] Isolated yields.

[c] Compound **1a** (3 mmol) and 2-Cl-AQN (0.1 equiv) in ethyl acetate (30 mL) were stirred and irradiated externally with a fluorescent lamp under oxygen atmosphere at room temperature for 15 h.



Scheme 2. Plausible reaction mechanism.

In conclusion, we report a novel and practical method for the preparation of diacylamines by the aerobic photo-oxidation of amides in the presence of the catalytic amount of 2-Cl-AQN under visible-light irradiation. This oxidation is a facile and convenient method from the viewpoint of synthetic organic chemistry and is relevant from a green chemistry perspective.

Acknowledgments

This work was supported by Grant-in-Aid for Young Scientists (B) (No. 24790015) from the Japan Society for the Promotion of Science (JSPS).

References and notes

1. Potts, K. T. *Chem. Rev.* **1961**, *61*, 87–127.
2. Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944–1945.
3. Wu, L.; Burgess, K. *J. Am. Chem. Soc.* **2008**, *130*, 4089–4096.
4. Klinge, M.; Cheng, H.; Zabriskie, T. M.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1379–1380.
5. Baburao, K.; Costello, A. M.; Petterson, R. C.; Sander, G. E. *J. Chem. Soc. C* **1968**, 2779–2781.
6. LaLonde, R. T.; Davis, C. B. *J. Org. Chem.* **1970**, *35*, 771–774.
7. Dunbar, R. E.; Swenson, W. M. *J. Org. Chem.* **1958**, *23*, 1793–1794.
8. Atanassova, I. A.; Petrov, J. S.; Ognjanova, V. H.; Mollov, N. M. *Synth. Commun.* **1990**, *20*, 2083–2090.
9. Seiller, B.; Heins, D.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 10901–10912.
10. (a) Tanaka, K.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1987**, *35*, 364–369; (b) Yoshifuji, S.; Tanaka, K.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873–3878; (c) Yoshifuji, S.; Arakawa, Y. *Chem. Pharm. Bull.* **1989**, *37*, 3380–3381.
11. Xu, L.; Zhang, S.; Trudell, M. L. *Chem. Commun.* **2004**, 1668–1669.
12. (a) Jin, Z.; Xu, B.; Hammond, G. B. *Tetrahedron Lett.* **2011**, *52*, 1956–1959; (b) Jin, Z.; Xu, B.; DiMagno, S. G.; Hammond, G. B. *J. Fluorine Chem.* **2012**, *143*, 226–230.
13. (a) Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 2671–2676; (b) Wang, J.-R.; Liu, L.; Wang, Y.-F.; Zhang, Y.; Deng, W.; Guo, Q.-X. *Tetrahedron Lett.* **2005**, *46*, 4647–4651.
14. Doumaux, A. R. J.; McKeon, J. E.; Trecker, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3992–3993.
15. Murata, S.; Miura, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1259–1262.
16. Huang, W.; Xu, M.-L. *J. Chem. Res.* **2013**, 77–79.
17. Nicolaou, K. C.; Mathison, C. J. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 5992–5997.
18. (a) Ochiai, M.; Kajishima, D.; Sueda, T. *Tetrahedron Lett.* **1999**, *40*, 5541–5544; (b) Sueda, T.; Kajishima, D.; Goto, S. *J. Org. Chem.* **2003**, *68*, 3307–3310.
19. Chern, C.-Y.; Huang, Y.-P.; Kan, W. M. *Tetrahedron Lett.* **2003**, *44*, 1039–1041.
20. Nakayama, H.; Itoh, A. *Synlett* **2008**, 675–678.
21. Tada, N.; Itoh, A. *Tetrahedron Lett.* **2010**, *51*, 6098–6100.
22. (a) Tada, N.; Hattori, K.; Nobuta, T.; Miura, T.; Itoh, A. *Green Chem.* **2011**, *13*, 1669–1671; (b) Cui, L.; Furuhashi, S.; Tachikawa, Y.; Tada, N.; Miura, T.; Itoh, A. *Tetrahedron Lett.* **2013**, *54*, 162–165; (c) Matsusaki, Y.; Yamaguchi, T.; Tada, N.; Miura, T.; Itoh, A. *Synlett* **2012**, 2059–2062; (d) Tada, N.; Ikebata, Y.; Nobuta, T.; Hirashima, S.; Miura, T.; Itoh, A. *Photochem. Photobiol. Sci.* **2012**, *11*, 616–619; (e) Cui, L.; Tada, N.; Okubo, H.; Miura, T.; Itoh, A. *Green Chem.* **2011**, *13*, 2347–2350.
23. *A typical procedure (entry 1) follows:* A dry EtOAc solution (3 mL) of the *N*-benzylacetamide (**1a**, 0.3 mmol), 2-Cl-AQN (0.03 mmol) in a pyrex test tube equipped with an O_2 balloon, was irradiated for 30 h with four 22 W fluorescent lamps, which were set up at a distance of 65 mm. The reaction mixture was concentrated under reduced pressure, and the pure product was obtained by preparative TLC or flash silicagel chromatography.
24. 2-Chloroanthraquinone absorbs light of wavelengths shorter than 450 nm, and the fluorescent lamp radiates visible light of wavelengths longer than 400 nm. Thus, 2-chloroanthraquinone absorbs light between 400 and 450 nm.