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PhIO/Bu_4NI mediated oxidative cyclization of amidoalkylation adducts for the synthesis of *N*-benzoyl aziridines and oxazolines

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Dedicated to Professor Lixin Dai on the occasion of his 85th birthday

ABSTRACT

An efficient oxidative cyclization of amidoalkylation adducts of activated methylene compounds with the combination of iodosobenzene and a catalytic amount of tetrabutylammonium iodide under neutral conditions is reported. The reaction affords *N*-benzoyl aziridines or oxazolines in moderate to excellent yields.

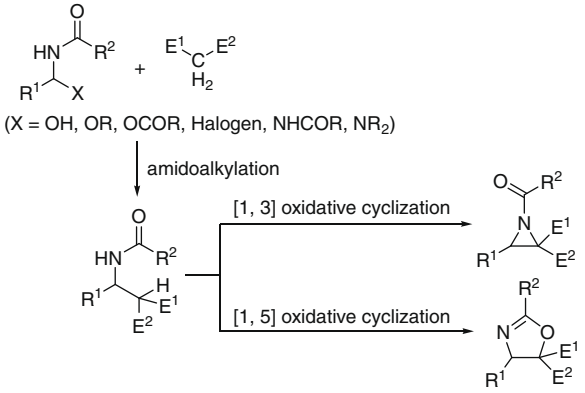
Among heterocycles, aziridines and oxazolines have attracted a lot of interest.[1,2] As the core structures, they are frequently found in a variety of biologically active natural molecules and pharmaceuticals. Meanwhile, they are widely used as synthetic intermediates, ligands, or chiral pools in organic synthesis. Consequently, it is desirable to search for new efficient methods for the construction of aziridine and oxazoline derivatives. In the past decades, amidoalkylations have been developed as a valuable alternative to the Mannich reaction, and significant advances have been made.[3,4] α-Amidoalkylation of activated methylene compounds provides ready access to β-amino dicarbonyl compounds,[5] which are proposed to be ready to undergo a [1, 3] or [1, 5] oxidative cyclization to generate *N*-acyl aziridines or oxazolines, which are normally required to be prepared from the corresponding amino alcohols (Scheme 1).[6]

As part of a program aimed at developing synthetic application of hypervalent iodine compounds,[7] some of our recent efforts have been addressed in the iodine(III)-induced oxidative cyclizations of Michael adducts for the construction of functionalized cyclopropanes[7e] and oxetanes.[7a] In the current study, we have sought to further extend the utility of this process by exploring the oxidative cyclization of α-amidoalkylation adducts of activated methylene compounds, which were prepared with *N*-(α-benzotriazolyl-alkyl)amides, developed by the Katritzky group, as the amidoalkylation reagents under the literature conditions (Scheme 2).[5]

The α-amidoalkylation adducts of diethyl malonate **1a** were utilized as the model substrate to search for suitable reaction conditions. The preliminary survey indicated that the oxidative cyclization of **1a** occurred in the presence of 2 equiv of PhIO and 2 equiv of Bu_4NI in THF at room temperature to afford *N*-benzoyl aziridine **2a** in 78% yield (Scheme 3). As one of the byproducts, oxazoline **3a** was isolated in 4% yield.

Further investigation revealed that the best ratio among substrate, PhIO, and Bu_4NI was 1:1.5:0.5, in which the yield of **2a** increased to 88% (Table 1, entry 4). The reaction still proceeded smoothly when 0.1 equiv of Bu_4NI was used (Table 1, entry 5). Control experiment showed that no aziridine was formed in the absence of Bu_4NI (Table 1, entry 6). The oxidative cyclization could be carried out in various organic solvents except in methanol (Table 1, entries 7–11). When the reaction was carried out in an air-open system with water as the solvent, *N*-benzoyl aziridine **2a** was obtained in 64% yield (Table 1, entry 12).

Compared with the normally used *N*-sulfonyl aziridines, *N*-benzoyl aziridines showed a better reactivity in the enantioselective



Scheme 1. Oxidative cyclization of amidoalkylation adducts.

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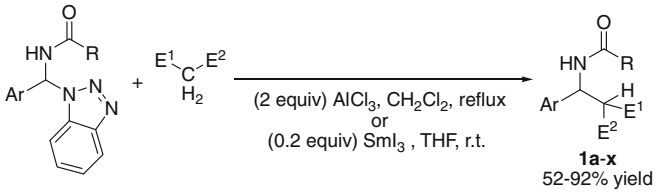
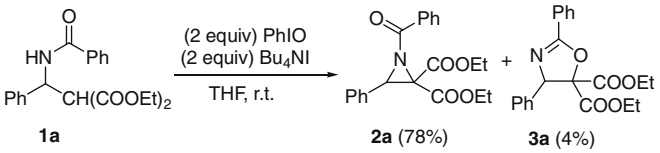


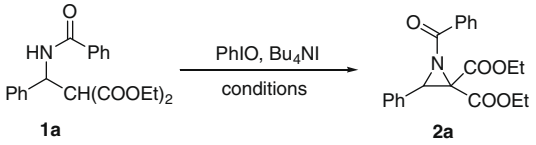
Scheme 2. α-Amidoalkylation of activated methylene compounds.



Scheme 3.

ring-opening reactions to afford useful optically active amines.[8] Motivated by the synthetic potential of the possible method, the scope of this reaction was then investigated under optimized conditions. In most of the cases, the reaction was completed in 10 min. An electronic substrate effect was observed. Compounds with an electron-withdrawing substituent were better substrates than those with an electron-donating substituent, and their reactions afforded the corresponding *N*-benzoyl aziridines in good to excellent yields. For example, the reaction of *p*-CH_3-substituted substrate afforded *N*-benzoyl aziridine **2h** in 52% yield (Table 2, entry 8), while the reaction of *p*-F- or *p*-NO_2-substituted substrate afforded the corresponding product **2e** or **2g** in 75% or 87% yield, respectively (Table 2, entries 5 and 7). The position of the electron-donating substituent also had an effect on the reaction. While moderate yields were obtained from the reactions of *o*- or *m*-BnO-substituted compound **1i** or **1j**, the reaction of *p*-BnO-substituted substrate **1k** was complex, and the expected product was not stable enough to be purified, albeit the formation of aziridine was detected by ^{1}H NMR spectroscopy of the crude product (Table 2, entries 9–11). With respect to the α-amidoalkylation adducts of other malonates, reaction of the dimethyl derivative **1n** gave rise to product **2n** in a moderate yield, while no reaction occurred with the sterically hindered di-*tert*butyl malonate derivative as the sub-

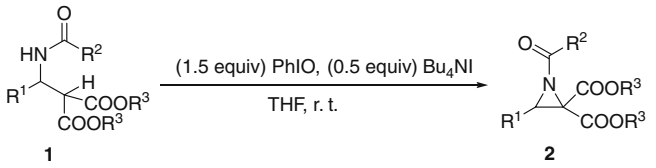
Table 1
Evaluation of reaction conditions[a]



Entry	PhIO (equiv)	Bu_4NI (equiv)	Solvent	**2a**[b] (%)
1	2	2	THF	78
2	1.5	1.5	THF	87
3	1.5	1	THF	86
4	1.5	0.5	THF	88
5	1.5	0.1	THF	80
6	1.5	0	THF	0
7	1.5	0.5	EtOAc	70
8	1.5	0.5	CH_3CN	66
9	1.5	0.5	$CHCl_3$	72
10	1.5	0.5	CH_2Cl_2	70
11	1.5	0.5	MeOH	Trace
12	1.5	0.5	H_2O	64

[a] The reactions were performed with **1a** (0.3 mmol), PhIO and Bu_4NI (as noted) in solvent (1 mL) at room temperature.
[b] Isolated yields.

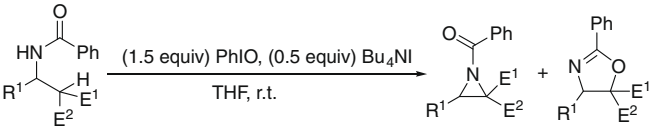
Table 2
Oxidative cyclization of amidoalkylation adducts of malonates[a]



Entry	R^1	R^2	R^3	**2**[b] (%)
1	C_6H_5	C_6H_5	CH_2CH_3	**2a** (88)
2	*o*-BrC_6H_4	C_6H_5	CH_2CH_3	**2b** (82)
3	*o*-ClC_6H_4	C_6H_5	CH_2CH_3	**2c** (80)
4	2,4-di-ClC_6H_3	C_6H_5	CH_2CH_3	**2d** (93)
5	*p*-FC_6H_4	C_6H_5	CH_2CH_3	**2e** (75)
6	*m*-$NO_2C_6H_4$	C_6H_5	CH_2CH_3	**2f** (91)
7	*p*-$NO_2C_6H_4$	C_6H_5	CH_2CH_3	**2g** (87)
8	*p*-$CH_3C_6H_4$	C_6H_5	CH_2CH_3	**2h** (52)
9	*o*-$BnOC_6H_4$	C_6H_5	CH_2CH_3	**2i** (50)
10	*m*-$BnOC_6H_4$	C_6H_5	CH_2CH_3	**2j** (70)
11	*p*-$BnOC_6H_4$	C_6H_5	CH_2CH_3	**2k**[c]
12	*p*-$CH_3OC_6H_4$	C_6H_5	CH_2CH_3	**2l**[c]
13	1-Naphthyl	C_6H_5	CH_2CH_3	**2m** (85)
14	C_6H_5	C_6H_5	CH_3	**2n** (46)
15	C_6H_5	C_6H_5	$C(CH_3)_3$	**2o** (0)
16	C_6H_5	CF_3	CH_2CH_3	**2p** (0)
17	C_6H_5	CH_3	CH_2CH_3	**2q** (0)
18	$CH_3CH_2CH_2$	C_6H_5	CH_2CH_3	**2y** (53)[d]

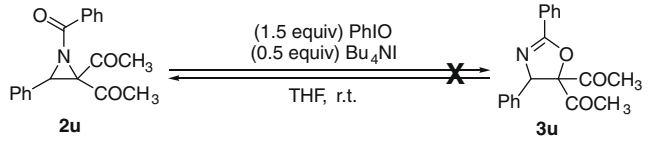
[a] The reactions were performed with substrate **1** (0.3 mmol), PhIO (0.45 mmol) and Bu_4NI (0.15 mmol) in anhydrous THF (1 mL) at room temperature.
[b] Isolated yields.
[c] The formation of aziridine was detected by the ^{1}H NMR of the crude product.
[d] Oxazoline **3y** was isolated in 27% yield.

Table 3
Oxidative cyclization of amidoalkylation adducts of active methylene compounds[a]

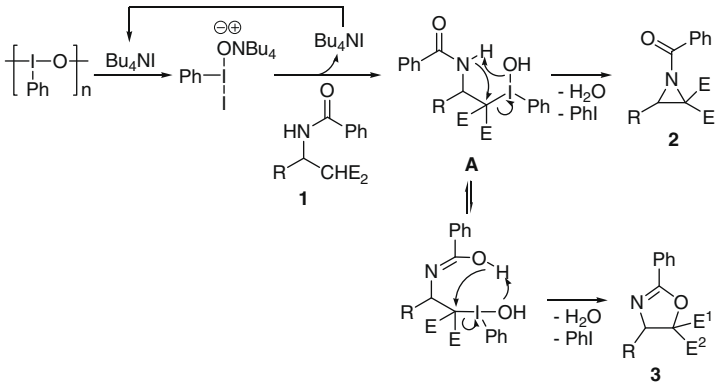


Entry	R^1	E^1	E^2	**2**[b] (%)	**3**[b] (%)
1	*p*-ClC_6H_4	CH_3CO	$COOCH_2CH_3$	**2r** (41)[c]	**3r** (33)[d]
2	*p*-ClC_6H_4	CH_3CO	$COOCH_3$	**2s** (45)[e]	**3s** (40)[f]
3	*p*-ClC_6H_4	CH_3CO	$COCH_3$	**2t** (12)	**3t** (60)
4	C_6H_5	CH_3CO	$COCH_3$	**2u** (12)	**3u** (62)
5	*o*-BrC_6H_4	CH_3CO	$COCH_3$	**2v** (19)	**3v** (50)
6	*p*-$NO_2C_6H_4$	CH_3CO	$COCH_3$	**2w** (14)	**3w** (52)
7	*p*-$CH_3C_6H_4$	CH_3CO	$COCH_3$	**2x** (13)	**3x** (78)
8	$CH_3CH_2CH_2$	CH_3CO	$COCH_3$	**2z** (8)	**3z** (42)

[a] The reactions were performed with substrate **1** (0.3 mmol), PhIO (0.45 mmol) and Bu_4NI (0.15 mmol) in anhydrous THF (1 mL) at room temperature.
[b] Isolated yields.
[c] The diastereoselectivity ratio of **2r**: cis/trans = 55:45 (determined by HPLC).
[d] The diastereoselectivity ratio of **3r**:cis/trans = 50:50.
[e] The diastereoselectivity ratio of **2s**:cis/trans = 60:40.
[f] The diastereoselectivity ratio of **3s**:cis/trans = 50:50.



Scheme 4.



Scheme 5. Plausible reaction pathway.

strate (Table 2, entries 14 and 15). When the benzoyl group on the nitrogen was replaced by an acetyl or trifluoroacetyl group, no oxidative cyclization was observed (Table 2, entries 16 and 17).

When diethyl 2-(1-benzamidobutyl)malonate (Table 2, entry 18) and α-amidoalkylation adducts of ethyl- or methyl-acetoacetate (Table 3, entries 1 and 2) were employed as the substrates, besides the expected *N*-benzoyl aziridines, the reactions also afforded the corresponding oxazolines. Further investigation revealed that the corresponding oxazolines were obtained as the major products in the cases of 2,4-pentanedione derivatives (Table 3, entries 3–8). A different electronic substrate effect was observed in the formation of oxazolines. Reactions of the electron-rich substrates showed a better selectivity for the formation of oxazolines than those of the electron-poor substrates.

N-benzoyl aziridine **2u** or oxazoline **3u** could not be converted into each other when they were treated with PhIO and Bu_4NI under the optimized reaction conditions (Scheme 4). A plausible reaction pathway for the PhIO/Bu_4NI mediated oxidative cyclization of amidoalkylation adducts of activated methylene compounds is outlined in Scheme 5. Polymeric iodosobenzene is depolymerized with Bu_4NI to generate a higher reactive iodine(III) species,[9] which reacts with the substrate **1** to form an intermediate **A** and regenerate Bu_4NI via a ligand-exchange reaction. After a [1, 3] or [1, 5] intramolecular nucleophilic displacement by the nitrogen or oxygen atom, the reaction affords the corresponding *N*-benzoyl aziridine or oxazoline accompanied by the reductive elimination of PhI.

In conclusion, we report here an efficient oxidative cyclization of amidoalkylation adducts of activated methylene compounds with the combination of iodosobenzene and a catalytic amount of Bu_4NI under neutral conditions.[10] The reaction affords *N*-benzoyl aziridines or oxazolines in moderate to excellent yields. The scope and synthetic application are ongoing and will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.069.

References and notes

1. For selected reviews, see: (a) Hou, X. L.; Wu, J.; Fan, R.; Ding, C. H.; Luo, Z. B.; Dai, L. X. *Synlett* **2006**, 181; (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701; (c) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905; (d) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247; (e) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 93; (f) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347; (g) Dodd, R. H. *Molecules* **2000**, *5*, 293; (h) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519; (i) Stamm, H. *J. Prakt. Chem.* **1999**, *4*, 319; (j) Jacobsen, E. N.. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 607; (k) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693; (l)*Comprehensive Heterocyclic Chemistry II*; Pearson, W. H., Lian, B. W., Bergmeier, S. C., Padwa, A., Eds.; Pergamon: Oxford, 1996; Vol. 1A, p 1; (m) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
2. For selected reviews, see: (a) Nicolaou, K. C.; Liazos, D. E.; Kim, D. W.; Schlawe, D.; De Noronha, R. G.; Longbottom, D. A.; Rodriguez, M.; Bucci, M.; Cirino, G. *J. Am. Chem. Soc.* **2006**, *128*, 4460; (b) Pirrung, M. C.; Tumey, L. N.; McClerren, A. L.; Ratz, C. R. H. *J. Am. Chem. Soc.* **2003**, *125*, 1575; (c) Bergeron, R. J.; Xin, M. G.; Weimar, W. R.; Smith, R. E.; Wiegand, J. *J. Med. Chem.* **2001**, *44*, 2469; (d) Clark, D.; Travis, D. A. *Bioorg. Med. Chem.* **2001**, *9*, 2857; (e) Onishi, H. R.; Pelak, B. A.; Gerckens, L. S.; Silver, L. L.; Kahan, F. M.; Chen, M. H.; Patchett, A. A.; Galloway, S. M.; Hyland, S. A.; Anderson, M. S.; Raetz, C. R. H. *Science* **1996**, *274*, 980; (f) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (g) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771; (h) Bergeron, R. J. *Chem. Rev.* **1984**, *84*, 587; (i) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270.
3. For selected reviews, see: (a) Zaugg, H. E. *Synthesis* **1984**, *85*, 181; (b) Tramontini, M. *Synthesis* **1973**, 703; (c) Zaugg, H. E. *Synthesis* **1970**, 49; (d) Zaugg, H. E.; Martin, W. B. *Org. React.* **1966**, *14*, 52.
4. For selected reviews, see: (a) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683; (b) Katritzky, A. R.; Yang, Z.; Cundy, D. J. *Aldrichim. Acta* **1994**, *27*, 31; (c) Katritzky, A. R.; Lan, X. *Chem. Soc. Rev.* **1994**, 363; (d) Katritzky, A. R.; Lan, X.; Fan, W. Q. *Synthesis* **1994**, 445; (e) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.
5. (a) Katritzky, A. R.; Pernak, J.; Fan, W. Q.; Saczewski, F. *J. Org. Chem.* **1991**, *56*, 4439; (b) Wang, X.; Mao, H.; Yu, Y.; Zhu, X.; Zhu, C. *Synth. Commun.* **2007**, *37*, 3751.
6. (a) Witte, M. D.; Horst, D.; Wiertz, E. J. H. J.; Van der Marel, G. A.; Overkleeft, H. S. *J. Org. Chem.* **2009**, *74*, 605; (b) Métro, T.-X.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 707; (c) Crosignani, S.; Swinnen, D. *J. Comb. Chem.* **2005**, *7*, 688; (d) Crosignani, S.; Young, A. C.; Linclau, B. *Tetrahedron Lett.* **2004**, *45*, 9611; (e) Gorunova, O. N.; Keuseman, K. J.; Goebel, B. M.; Kataeva, N. A.; Churakov, A. V.; Kuzmina, L. G.; Dunina, V. V.; Smoliakov, I. P. *J. Organomet. Chem.* **2004**, *689*, 2382; (f) Aggarwal, V. K.; Vasse, J.-L. *Org. Lett.* **2003**, *5*, 3987.
7. (a) Ye, Y.; Zheng, C.; Fan, R. *Org. Lett.* **2009**, *11*, 3156; (b) Fan, R.; Li, W.; Pu, D.; Zhang, L. *Org. Lett.* **2009**, *11*, 1425; (c) Fan, R.; Ye, Y. *Adv. Synth. Catal.* **2008**, *350*, 1526; (d) Fan, R.; Li, W.; Ye, Y.; Wang, L. *Adv. Synth. Catal.* **2008**, *350*, 1531; (e) Fan, R.; Ye, Y.; Li, W.; Wang, L. *Adv. Synth. Catal.* **2008**, *350*, 2488; (f) Fan, R.; Li, W.; Wang, B. *Org. Biomol. Chem.* **2008**, *6*, 4615; (g) Fan, R.; Pu, D.; Gan, J.; Wang, B. *Tetrahedron Lett.* **2008**, *49*, 4925; (h) Fan, R.; Pu, D.; Wen, F. *J. Org. Chem.* **2007**, *72*, 8994.
8. (a) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, L. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084; (b) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259; (c) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312; (d) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; (e) Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252; (f) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611.
9. (a) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431; (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123; (c) Zhdankin, V. V.; Stang, P. J. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; VCH: New York, 1999; p 327; (d) Grushin, V. V. *Chem. Soc. Rev.* **2000**, *29*, 315; (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523; (f) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997; (g) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893; (h) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.
10. *General experimental procedure and spectroscopic data*: A solution of α-amidoalkylation adduct **1** (0.3 mmol) in anhydrous THF was treated with PhIO (99 mg, 0.45 mmol) and Bu_4NI (55 mg, 0.15 mmol). The resulted mixture was stirred at 25 °C. After the substrate disappeared (determined by TLC), the mixture was concentrated and directly purified by flash column chromatography (10–20% ethyl acetate in hexane) to provide the corresponding *N*-benzoyl aziridine **2** or oxazoline **3**. *Diethyl 1-benzoyl-3-*

phenylaziridine-2,2-dicarboxylate **2a**: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.0 Hz, 2 H), 7.55 (t, J = 7.2 Hz, 1 H), 7.43–7.48 (m, 4 H), 7.34–7.41 (m, 3H), 4.49 (s, 1 H), 3.89–4.12 (m, 4 H), 1.00 (t, J = 6.9 Hz, 3 H), 0.82 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 164.1, 163.6, 133.1, 132.4, 132.2, 128.9, 128.8, 128.5, 128.4, 127.1, 62.8, 61.8, 54.5, 49.0, 13.5; IR (KBr) 3058, 2989, 2932, 1742, 1688, 1449, 1411, 1263 cm^{-1}; HRMS *m/z* calcd for $C_{21}H_{22}NO_5$ ([M+H]$^+$): 368.1498, found 368.1511. *1,1′-(2,4-diphenyl-4,5-dihydrooxazole-5,5-diyl)diethanone* **3t**: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.58 (m, 7 H), 7.37 (t, J = 7.5 Hz, 2H), 6.69 (s, 1H), 2.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 172.6, 156.8, 135.8, 135.2, 133.5, 132.4, 129.2, 128.7, 128.4, 127.5, 120.1, 93.7, 28.1, 13.2; IR (KBr) 3056, 2931, 2855, 1665, 1400, 1269 cm^{-1}; HRMS *m/z* calcd for $C_{19}H_{17}ClNO_3$ ([M+H]$^+$): 342.0897, found 342.0906.