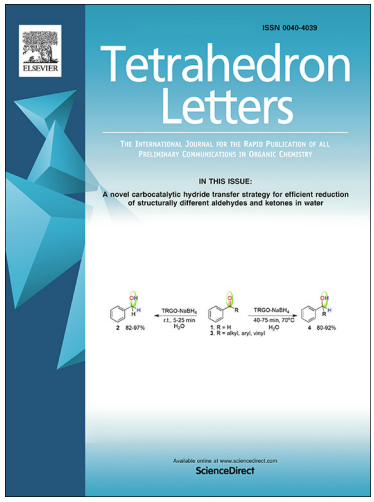


Reaction of *N*-methylazomethine ylide with aroyl azides: synthesis of imidazolidin-4-ones

Evgeny M. Buev, Vladimir S. Moshkin, Vyacheslav Y. Sosnovskikh

PII: S0040-4039(19)30119-4
DOI: https://doi.org/10.1016/j.tetlet.2019.02.010
Reference: TETL 50604

To appear in: *Tetrahedron Letters*

Received Date: 28 December 2018
Revised Date: 25 January 2019
Accepted Date: 4 February 2019

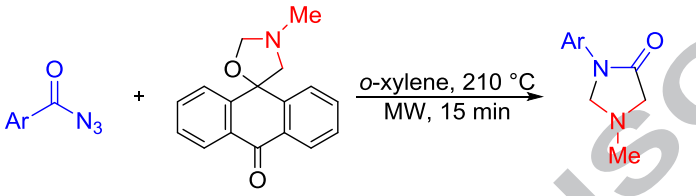
Please cite this article as: Buev, E.M., Moshkin, V.S., Sosnovskikh, V.Y., Reaction of *N*-methylazomethine ylide with aroyl azides: synthesis of imidazolidin-4-ones, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.02.010

Graphical Abstract

Reaction of *N*-methylazomethine ylide with aroyl azides: synthesis of imidazolidin-4-ones

Leave this area blank for abstract info.

Evgeny M. Buev, Vladimir S. Moshkin*, Vyacheslav Y. Sosnovskikh



Ar = Ph, 3-ClC_6H_4, 4-ClC_6H_4, 4-Cl-3-$NO_2C_6H_3$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 3-Pyridyl, Styryl

30–81% yield

* Corresponding author. Tel: +7 3433899597; e-mail: mvslc@mail.ru (V. S. Moshkin).

Reaction of *N*-methylazomethine ylide with aroyl azides: synthesis of imidazolidin-4-ones

Evgeny M. Buev, Vladimir S. Moshkin*, Vyacheslav Y. Sosnovskikh

Institute of Natural Sciences and Mathematics, Ural Federal University, 620000 Ekaterinburg, Russian Federation
** Corresponding author. Tel: +7 3433899597; e-mail: mvslc@mail.ru*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Nonstabilized azomethine ylide
[3+2]-Cycloaddition
Aroyl azides
Isocyanates

ABSTRACT

Aryl isocyanates generated *in situ* from aroyl azides react with *N*-methylazomethine ylide generated *in situ* from *N*-methylspiroanthraceneoxazolidine at 210 °C in a microwave reactor to form 3-arylimidazolidin-4-ones in 30–81% yield.

The [3+2]-cycloaddition of azomethine ylides is an attractive and useful tool for the construction of various azaheterocycles.[1] In particular, nonstabilized azomethine ylides are electron-rich 1,3-dipoles widely used in the synthesis of pyrrolidines from electron-deficient alkenes.[2] Also, they smoothly react with carbonyl dipolarophiles to give oxazolidine rings which are versatile intermediates in the synthesis of a wide range of heterocyclic compounds.[3]

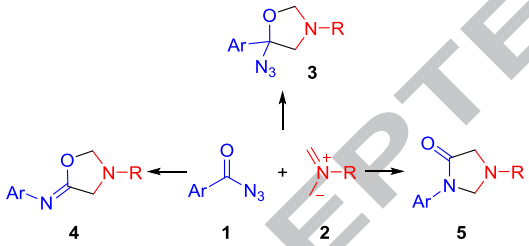
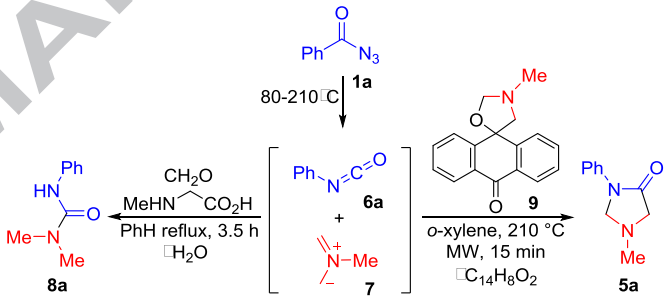


Figure 1. Possible directions for the reaction of aroyl azides and nonstabilized azomethine ylides.

In the course of our studies regarding azomethine ylide chemistry,[4] we were interested in how they can react with aroyl azides **1**. The latter are readily available and valuable reagents for the synthesis of amines, amides, ureas and isocyanates.[5] Due to the high reactivity of these compounds several directions could be assumed for their reaction with dipoles **2** (Fig. 1). Since nonstabilized azomethine ylides react with the carbonyl group of isatoic and phthalic anhydrides,[3] first, the possibility of cycloaddition to the C=O bond in acyl azides **1** and formation of an oxazolidine ring **3** could be expected at low temperatures. The second direction is a domino-sequence of Curtius rearrangement[6] and subsequent cycloaddition of the azomethine ylide to the formed aryl isocyanate. The chemoselectivity of the latter reaction is not clear and both oxazolidine **4** or imidazolidine **5** ring formation could be expected. To the best of our knowledge, there are only a few specific examples of the [3+2]-cycloaddition of stabilized azomethine ylides derived from aziridines with isocyanates in the literature.[7] Thus, an investigation of the reactivity of nonstabilized azomethine ylides with aroyl azides **1** is of interest.



Scheme 1. Reactions of benzoyl azide (**1a**).

We commenced our study by examining the model reaction of benzoyl azide (**1a**) with *N*-benzylazomethine ylide derived from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine[8] in the presence of catalytic TFA at room temperature. Mild conditions for ylide generation were chosen to reduce the rate of the Curtius rearrangement. Unfortunately, we found that this reaction resulted in a complex mixture of products probably due to the instability of 5-azidooxazolidine **3** (Table 1, entry 1). As expected, utilization of another classic method for the generation of ylide **7**, condensation of sarcosine and paraformaldehyde in benzene at reflux (80 C), should occur *via* the formation of phenyl isocyanate (**6a**) and subsequent [3+2]-cycloaddition (Scheme 1; Table 1, entry 2). Nevertheless, heating the reactants in benzene with a Dean-Stark trap for 3.5 h surprisingly gave fenuron (**8a**) (1,1-dimethyl-3-phenylurea) in 87% yield. Apparently, the formed phenyl isocyanate (**6a**) was not reactive in the 1,3-dipolar cycloaddition under these conditions, and the generated *N*-methylazomethine ylide (**7**) reacted with trace water to give dimethylamine. The latter readily reacted with isocyanate to form urea **8a**.

Taking into account previous results, the most favourable precursor of azomethine ylide **7** should allow the reaction to be carried out without the formation of water and at higher temperature. These requirements are in line with conditions recently proposed by us for spiro[anthracene–oxazolidine] system **9**, which undergoes cycloreversion to azomethine ylide upon heating in an anhydrous solvent.[9] Indeed, heating *N*-methylspiroanthraceneoxazolidine **9** at reflux with excess benzoyl azide (**1a**) in dry *o*-xylene for 4 h resulted in the

formation of imidazolidin-4-one **5a** contaminated by an admixture of starting oxazolidine **9** and traces of fenuron (**8a**) (Table 1, entry 3). At the same time, increasing the reaction temperature to 210 °C and heating the reagents in dry *o*-xylene in a microwave reactor under an argon atmosphere for 15 min increased the conversion of oxazolidine **9** into imidazolidine **5**[a] (Table 1, entry 4).

Table 1. Optimisation of the reaction conditions.

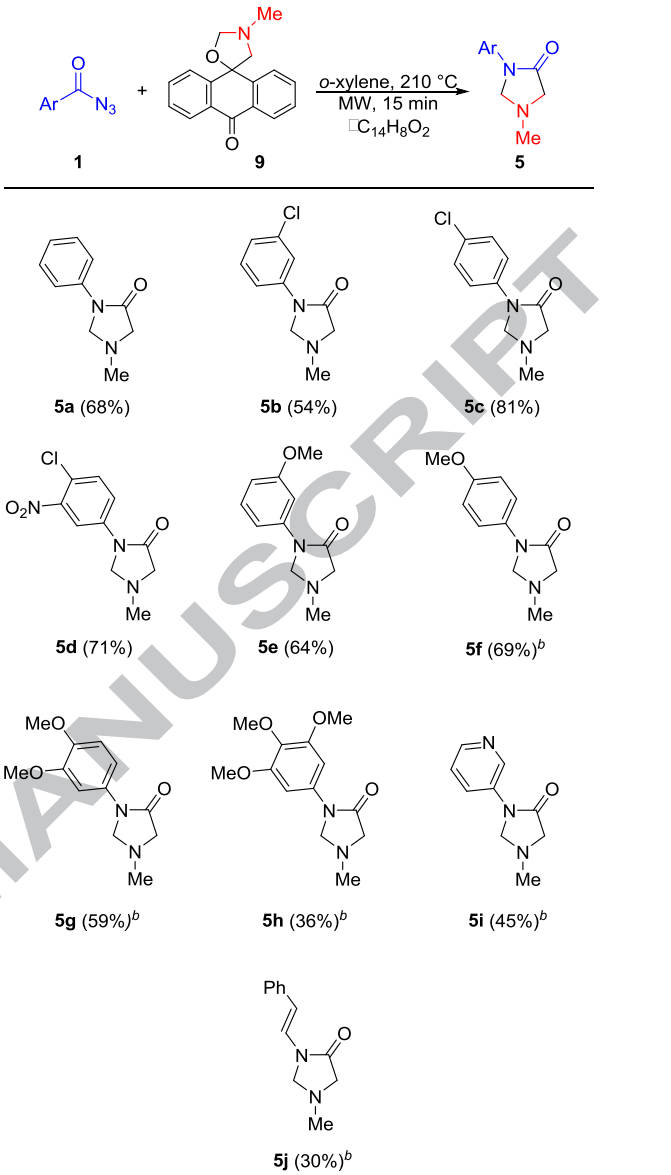
Entry	Conditions	Yield **5a**[a] (%)
1	**1a** (1 equiv.), *N*-(MeOCH$_2$)-*N*-(Me$_3$SiCH$_2$)benzylamine (1.05 equiv.), TFA (0.35 equiv.), CH$_2$Cl$_2$, 0–25 °C, 24 h	Complex mixture
2	**1a** (1 equiv.), sarcosine (1.2 equiv.), CH$_2$O (1.8 equiv.), PhH, reflux, 3.5 h	**8a** (87%)
3	**1a** (1.4 equiv.), **9** (1.0 equiv.), *o*-xylene, reflux, 4 h	–[b]
4	**1a** (1 equiv.), **9** (1.1 equiv.), *o*-xylene, MW, 210 °C, 15 min	–[c]
5	**1a** (1.3 equiv.), **9** (1 equiv.), *o*-xylene, MW, 210 °C, 15 min	–[d]
6	**1a (1.5 equiv.), 9 (1 equiv.), *o*-xylene, MW, 210 °C, 15 min**	**68**[e]
7	**1a** (1.5 equiv.), **9** (1 equiv.), MW, 210 °C, 15 min	42[f]

[a] Yield after the acidic extraction of bases from the crude mixture with 1.5M HCl, subsequent neutralization with NaHCO$_3$, and extraction with PhMe. [b] Mixture of **5a:9:8a** (NMR ratio 8:3:1). [c] Mixture of **5a:9:8a** (NMR ratio 13:7:1). [d] Product was contaminated by starting oxazolidine **9**. [e] Product was purified from traces of fenuron **8a** by dissolution in a mixture of Et$_2$O/hexane. [f] Product was purified by column chromatography.

Unfortunately, the product was also contaminated by traces of spiroanthraceneoxazolidine **9**. To overcome this circumstance a simple modification, consisted of using of 1.5 equiv. of benzoyl azide (**1a**), was applied (Table 1, entry 6). Gratifyingly, 1-methyl-3-phenylimidazolidin-4-one (**5a**) was isolated in 68% yield.[10,11] It should be noted that imidazolidin-4-one **5a** could be readily isolated from the crude mixture by converting it into the corresponding water-soluble hydrochloride with subsequent extraction of non-basic admixtures by PhMe and basification with NaHCO$_3$. As a side note, we also managed to carry out the reaction of benzoyl azide (**1a**) and spirooxazolidine **9** under solvent-free conditions and product **5a** was obtained in 42% yield after chromatographic purification (Table 1, entry 7). It should be noted that such 3-arylimidazolidin-4-ones **5** were previously synthesized by the cyclization of glycinamides and were reported as muscular relaxants and antirheumatic agents.[12]

With the optimized conditions in hand, we investigated the influence of substituents on the aromatic ring (Table 2). Gratifyingly, aroyl azides **1** bearing chlorine substituents in the *meta*- and *para*-positions reacted with spiro[anthracene–oxazolidine] **9** to give 3-(chlorophenyl)-1-methylimidazolidin-4-ones **5b** and **5c** in 54% and 81% yield, respectively.[11] Insertion of an additional electron-withdrawing NO$_2$ group in the *meta*-position did not affect the reaction and imidazolidine **5d** was isolated in 71% yield. Electron-donating methoxy groups were tolerated and cycloadducts **5e** and **5f** were obtained in 64% and 69% yield, respectively. In contrast, increasing the number of electron-donating groups in the aromatic moiety of aroyl azide **1** decreased the yield of 3-arylimidazolidines **5g** and **5h** (59% and 36%, respectively). Nicotinoyl azide obtained from nicotinic acid also reacted with *N*-methylspiroanthraceneoxazolidine **9** in moderate yield to give **5i** (45%).[11]

Table 2. Synthesis of 1-methyl-3-arylimidazolidin-4-ones **5a–j**.[a]

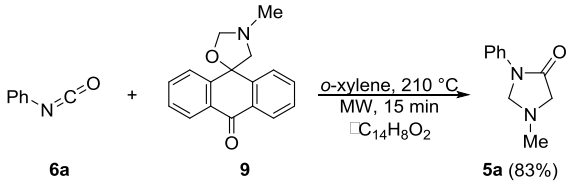


[a] Reagents and conditions: aroyl azide **1** (1.5 equiv.), spiroanthraceneoxazolidine **9** (1 equiv.), dry *o*-xylene, MW, 210 °C, 15 min. [b] Isolated yields of chromatographically purified compounds **5f–j** are specified.

Interestingly, cinnamoyl azide, which possesses two reactive groups, namely, an acyl azide and activated double carbon-carbon bond, reacted chemoselectively to give enamide **5j** in 30% yield. Signals of the pyrrolidine ring were not found in the ^{1}H NMR spectrum of the crude product. Obviously, this is due to the fact that Curtius rearrangement starts at a lower temperature than the elimination of azomethine ylide from spiroanthraceneoxazolidine **9**.

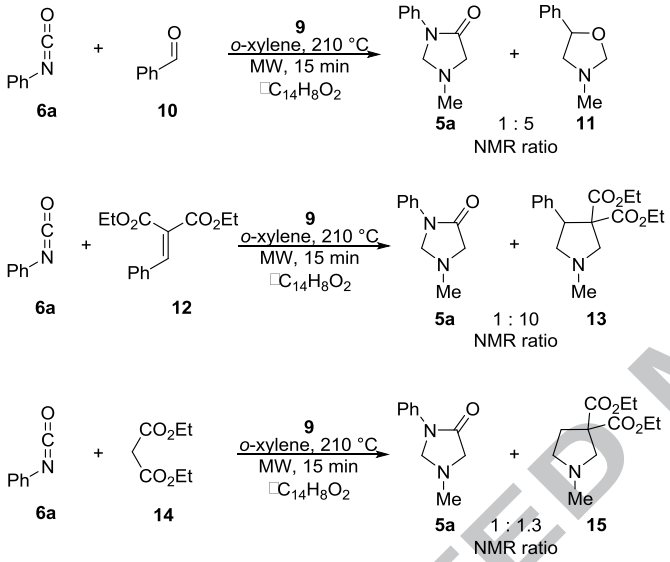
The reaction of bulky pivaloyl azide did not result in the cycloaddition product, probably, due to the inactivity of azomethine ylide to the sterically hindered C=N moiety of the formed isocyanate. Notably the reaction also did not occur with more sterically available C=O group of the isocyanate.

In view of the fact that the probable intermediate of this reaction is an aryl isocyanate, we performed the reaction of phenyl isocyanate **6a** with spiroanthraceneoxazolidine **9** (phenyl isocyanate **6a** (1.5 equiv.), **9** (1 equiv.), *o*-xylene, MW, 210 °C, 15 min). As expected, the reaction proceeded *via* [3+2]-cycloaddition of *N*-methylazomethine ylide at the C=N group and gave imidazolidin-4-one **5a** in 83% yield (Scheme 2).



Scheme 2. Reaction of phenyl isocyanate **6a** with spiroanthraceneoxazolidine **9**.

Despite the considerable amount of examples of the cycloadditions of nonstabilized azomethine ylides to carbonyl compounds in the literature,[3] the number of cycloadditions to imines are limited.[13] Considering the obtained results for the reactivity of isocyanates, which possess both C=O and C=N groups, we were interested in the comparing the reactions of isocyanates with other dipolarophiles towards *N*-methylazomethine ylide (**7**).



Scheme 3. Comparison of the reactivity of phenyl isocyanate and different dipolarophiles.

As a model system we chose the reaction of equimolar amounts of phenyl isocyanate (**6a**), spiro[anthracene–oxazolidine] **9** and another dipolarophile using the optimised conditions for the [3+2]-cycloaddition to isocyanates (*o*-xylene, MW, 210 C, 15 min). Thus, benzaldehyde (**10**) is a well-known C=O dipolarophile that reacts with the azomethine ylide derived from precursor **9** to give 5-phenyloxazolidine **11** in 73% isolated yield.[9] Heating the mixture of isocyanate **6a** and benzaldehyde **10** with the source of nonstabilized azomethine ylide **9** resulted in a mixture of imidazolidine **5a** and oxazolidine **11** in NMR ratio 1 : 5, respectively (Scheme 3). Under the same conditions, heating diethyl 2-benzylidenemalonate **12** as a classical C=C dipolarophile with isocyanate **6a** gave a mixture of products with the predominance of diethyl 1-methyl-4-phenylpyrrolidine-3,3-dicarboxylate **13** (NMR ratio **5a** : **13** 1 : 10). Remarkably, azomethine ylide **7** possesses diverse reactivity and it is able to act not only as a dipole but also as a base and a source of iminium cation.[14] Thus, we performed a more complicated comparison consisting of heating N=C=O dipolarophile **6a** and CH-acidic diethyl malonate **14**. This experiment resulted in an almost equal mixture of imidazolidine **5a** and diethyl pyrrolidine-3,3-dicarboxylate **15** (NMR ratio 1 : 1.3). The latter result shows that the reactivity of ylide **7** as a base and as a dipole toward a low reactivity isocyanate is comparable. At the same time, it showed better reactivity with C=O and C=C dipolarophiles than with N=C=O.

In conclusion, we developed a new reaction for the synthesis of 3-arylimidazolidin-4-ones **5** from aroyl azides **1** and spiro[anthracene-oxazolidine] **9** *via in situ* generation of the two intermediates – aryl isocyanates and nonstabilized *N*-methylazomethine ylide. To the best of our knowledge, the observed process is a unique example of the conversion of an oxazolidine ring to an imidazolidine core. The results obtained reveal new aspects of the diverse azomethine ylides reactivity and further investigation of the reactions of these ylides is underway in our laboratory and will be reported in due course.

Acknowledgments

The reported study was funded by RFBR according to the research project № 18-33-00042. We also thank Sergey Usachev for his remarks.

References and notes

1. (a) O. Tsuge, S. Kanemasa, Adv. Heterocycl. Chem. 45 (1989) 231; (b) L.M. Harwood, R.J. Vickers, in: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, Chemistry of Heterocyclic Compounds, Vol. 59 (Eds.: A. Padwa and W.H. Pearson), Wiley: Chichester, 2002, p. 169.
(a) R. Grigg, S. Thianpatanagul, J. Chem. Soc., Chem. Commun. (1984) 180; (b) C. Nájera, J.M. Sansano, Curr. Org. Chem. 7 (2003) 1105; (c) I. Coldham, R. Hufton, Chem. Rev. 105 (2005) 2765; (d) V.S. Moshkin, V.Y. Sosnovskikh, P.A. Slepukhin, G.-V. Röschenthaler, Mendeleev Commun. 22 (2012) 29;(e) J.H. Ryan, Arkivoc part i (2015) 160; (f) H.A. Döndas, M. de Gracia Retamosa, J.M. Sansano, Synthesis 49 (2017) 2819.
2. A.G. Meyer, J.H. Ryan, Molecules 21 (2016) 935.
(a) V.Y. Sosnovskikh, M.Y. Kornev, V.S. Moshkin, E.M. Buev, Tetrahedron 70 (2014) 9253; (b) E.M. Buev, V.S. Moshkin, V.Y. Sosnovskikh, Tetrahedron Lett. 56 (2015) 6590; (c) A.V. Pavlushin, V.S. Moshkin, V.Y. Sosnovskikh, Mendeleev Commun. 27 (2017) 628.
5. (a) W. Lwowski, in: The Azido Group, (Ed.: S. Patai), John Wiley & Sons Ltd.: Chichester, 1971, p. 503; (b) E.F.V. Scriven, K. Turnbull, Chem. Rev. 88 (1988) 297; (c) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, Angew. Chem. Int. Ed. 44 (2005) 5188; (d) Organic Azides: Syntheses and Applications, (Eds.: S. Bräse, K. Banert), John Wiley & Sons Ltd.: Chichester, 2010.
6. (a) G. L'abbé, Chem. Rev. 69 (1969) 345; (b) D.V. Banthorpe, in: The Azido Group, (Ed.: S. Patai), John Wiley & Sons Ltd.: Chichester, 1971, p. 397.
7. (a) H. Benhaoua, F. Texier, R. Carrié, Tetrahedron 42 (1986) 2283; (b) H. Benhaoua, F. Texier, L. Toupet, R. Carrié, Tetrahedron 44 (1988) 1117; (c) O. Mamoun, H. Benhaoua, Bull. Soc. Chim. Belg. 103 (1994) 753; (d) K. Zhang, P.R. Chopade, J. Louie, Tetrahedron Lett. 49 (2008) 4306.
8. Y. Terao, H. Kotaki, N. Imai, K. Achiwa, Chem. Pharm. Bull. 33 (1985) 896.
9. E.M. Buev, V.S. Moshkin, V.Y. Sosnovskikh, Org. Lett. 18 (2016) 1764.
10. *General procedure for the preparation of 1-methyl-3-arylimidazolidin-4-ones **10a–i**.* A 10 mL microwave reaction tube was charged with a stirrer bar, the corresponding aroyl azide **1** (1.5 mmol), 3′-methyl-10*H*-spiro[anthracene-9,5′-oxazolidin]-10-one (**9**) (1.0 mmol) and dry *o*-xylene (2 mL). The vial was purged with an argon atmosphere and sealed with a cap. After pre-stirring for 3 min, the mixture was heated in a microwave reactor at 210 °C for 15 min with stirring. (Caution! Rapid evaluation of N_2 starts at 100–120 °C. High pressure in the vial.). After cooling with a compressed air flow, the resulting mixture was diluted with PhMe (5 mL). The precipitated anthraquinone was filtered off. The solution was extracted with cold 1.5 M HCl (10 mL), and the aqueous phase was washed with PhMe (2 × 5 mL). The aqueous layer was basified with $NaHCO_3$ to pH 8, and extracted with PhMe (2 × 5 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to give the desired product. Imidazolidinones **5f–j** was purified by column chromatography (eluent: chloroform/ethanol). Product **5h** was additionally purified from trace amounts of urea by dissolution in warm Et_2O, urea was crystallized by addition of hexane, filtered off, washed with hexane, and solvents were evaporated in vacuo to give 3-arylimidazolidin-4-one **5h**.

11. *1-Methyl-3-phenylimidazolidin-4-one (**5a**).* Yellow solid, 68% yield, mp 53−55 °C (previously reported as the hydrochloride salt mp 188 °C; ref. 12). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.6, 0.9 Hz, 2H, 2,6-HPh), 7.38 (t, J = 8.0 Hz, 2H, 3,5-HPh), 7.17 (t, J = 7.4 Hz, 1H, 4-HPh), 4.55 (s, 2H, 2-CH_2), 3.45 (s, 2H, 5-CH_2), 2.54 (s, 3H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 137.5, 129.2, 125.1, 119.4, 72.3, 59.0, 41.7. HRMS (ESI) calcd for $(C_{10}H_{13}N_2O)^+$ $[M+H]^+$: 177.1022, found: 177.1027.
*3-(4-Chlorophenyl)-1-methylimidazolidin-4-one (**5c**).* Yellow solid, 81% yield, mp 78−79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 9.1 Hz, 2H, Ar), 7.33 (d, J = 9.1 Hz, 2H, Ar), 4.52 (t, J = 0.8 Hz, 2H, 2-CH_2), 3.44 (t, J = 0.8 Hz, 2H, 5-CH_2), 2.53 (s, 3H, NCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 136.1, 130.1, 129.2, 120.4, 72.2, 58.9, 41.6. HRMS (ESI) calcd for $(C_{10}H_{12}ClN_2O)^+$ $[M+H]^+$: 211.0633, found: 211.0638.
*1-Methyl-3-(pyridin-3-yl)imidazolidin-4-one (**5i**).* Product **5i** was synthesized according to the general procedure except for the reaction work-up. After microwave heating and compressed air flow cooling, the resulting mixture was diluted with a mixture of PhMe/hexane (2:1, 8 mL) and the precipitated solid anthraquinone was filtered off. The solvents were evaporated *in vacuo* and the crude product was isolated by column chromatography (eluent: chloroform/ethanol 100/4; R_f (chloroform/ethanol, 100/10) = 0.36). Viscous yellow oil, 45% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 2.5 Hz, 1H, 2-HPy), 8.42 (dd, J = 4.8, 1.2 Hz, 1H, 4-HPy), 8.20 (ddd, J = 8.4, 2.5, 1.2 Hz, 1H, 6-HPy), 7.33 (dd, J = 8.4, 4.8 Hz, 1H, 5-HPy), 4.58 (s, 2H, 2-CH_2), 3.46 (s, 2H, 5-CH_2), 2.56 (s, 3H, NCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 145.5, 139.4, 134.7, 126.9, 124.0, 71.6, 58.7, 41.6. HRMS (ESI) calcd for $(C_9H_{12}N_3O)^+$ $[M+H]^+$: 178.0975, found: 178.0978.
12. J. Hellerbach, US Patent 3428646, 1969.
13. (a) J. Chastanet, G. Roussi, J. Org. Chem. 53 (1988) 3808; (b) C. Izquierdo, F. Esteban, J.L.G. Ruano, A. Fraile, J. Alemán, Org. Lett. 18 (2016) 92; (c) J.K. Laha, K.P. Jethava, K.S.S. Tummalapalli, S. Sharma, Eur. J. Org. Chem. (2017) 4617; (d) M. Beuvin, M. Manneveau, S. Diab, B. Picard, M. Sanselme, S.R. Piettre, J. Legros, I. Chataigner, Tetrahedron Lett. 59 (2018) 4487.
14. E.M. Buev, V.S. Moshkin, V.Y. Sosnovskikh, J. Org. Chem. 82 (2017) 12827.

Supplementary data

Supplementary data associated with this article can be found in the online version.