Mesoionic Dipoles

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Development and Cycloaddition Reactivity of a New Class of Pyridine-Based Mesoionic 1,3-Dipole

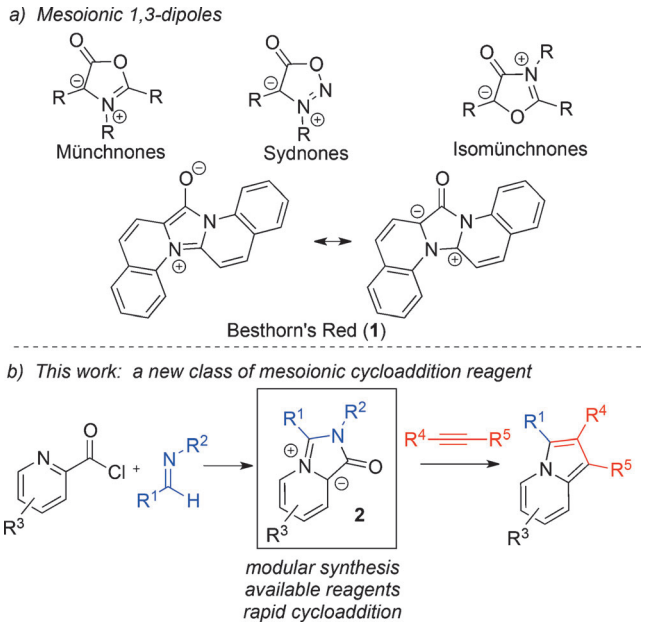
*Huseyin Erguven, David C. Leitch, Evan N. Keyzer, and Bruce A. Arndtsen**

Abstract: *We describe here the development and structural characterization of a new type of mesoionic 1,3-dipole, which can be generated in the one-step reaction of imines with pyridine- or quinoline-based acid chlorides. Coupling the formation of these dipoles with alkyne cycloaddition can open a general and modular route to synthesize indolizines from combinations of available and diversifiable building blocks.*

1,3-Dipolar cycloaddition has become one of the central synthetic approaches to construct five-membered ring heterocycles.[1] Relative to the more classical assembly of heterocycles by cyclization of pre-synthesized substrates, dipolar cycloadditions can provide access to these products in a convergent fashion, where one reactant is often a readily available unsaturated dipolarophile (alkyne, alkene, imine, etc). These cycloadditions can also be rapid reactions, which, when coupled with the orthogonality of this chemistry to more traditional organic reactions, has opened its application in a diverse array of areas (i.e. a variant of "click" reactions).[2] Examples include not just organic heterocycle synthesis, but also biochemical studies,[3] polymer chemistry,[4] materials science,[5] and many other topics.

Key to the utility of 1,3-dipolar cycloaddition is access to these reactive dipoles, many of which were pioneered through the early work of Huisgen and others.[6] One notable class are mesoionic heterocycles (e.g. Scheme 1 a).[7] In contrast to many 1,3-dipoles, mesoionic dipoles can be considered of "intermediate" ionicity, and multiple aromatic resonance structures can be drawn for each of these compounds. An important feature of mesoionic heterocycles is their stability, where resonance can make many of these reagents sufficiently robust for isolation. Nevertheless, the use of many variants of mesoionics can be limited by the required steps needed to build-up their structure, which can detract from their utility in heterocycle synthesis.

We have recently become interested in the design of new classes of mesoionic dipoles, and in particular those that might be more easily generated from available substrates.[8] In considering potential structures, we noted that one of the earliest isolated mesoionic heterocycles was quinoline-based compound **1** (Scheme 1 a), commonly known as Besthorn's Red. This red pigment was generated by Besthorn in 1894,[9]



Scheme 1. Mesoionic 1,3-dipoles and cycloaddition.

with subsequent studies by Krollpfeiffer[10] demonstrating it to contain the now accepted mesoionic structure. Besthorn's Red has not been shown to participate in 1,3-dipolar cycloaddition reactivity, presumably due to its extended conjugation and resonance stabilization. Nevertheless, in light of its facile synthesis from quinolines, we questioned if this platform might be modified to access to an alternative class of mesoionic 1,3-dipolar cycloaddition reagents. We describe here our studies towards this goal. These demonstrate that the reaction of imines with pyridine-based acid chlorides can allow the generation of a new type of 1,3-dipolar cycloaddition reagent **2** (Scheme 1 b). Compounds **2** undergo rapid 1,3-dipolar cycloaddition reactions with alkynes. The latter opens a route to construct families of pharmaceutically relevant indolizines,[11] where this structure is generated in one pot from simply imines, heterocyclic acid chlorides, and alkynes.

Our initial studies probed the reaction of the acid chloride of picolinic acid (**3a**) with the imine *p*-tolyl(H)C=NBn (Scheme 2). Combining these reagents at 80 °C leads to formation of a green solution over the course of 12 h, suggestive of the potential formation of the chromophoric 1,3-dipole. However, ^{1}H NMR analysis shows this reaction is not clean, and includes the formation of significant amounts of protonated imine and other products. After testing several reaction conditions, it was found that simple Et_3N can serve as an effective base for this transformation, and leads to the near

[*] H. Erguven, D. C. Leitch, E. N. Keyzer, Prof. B. A. Arndtsen
Department of Chemistry, McGill University
801 Sherbrooke St. W, Montreal, Quebec, H3A 0B8 (Canada)
E-mail: bruce.arndtsen@mcgill.ca
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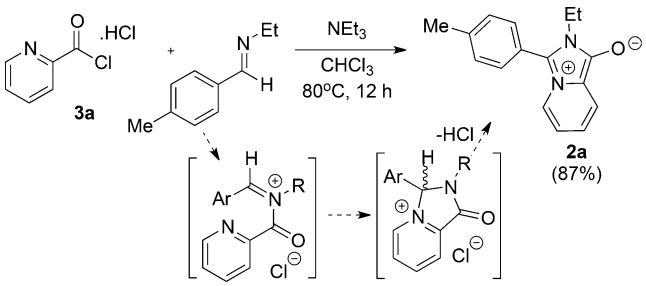


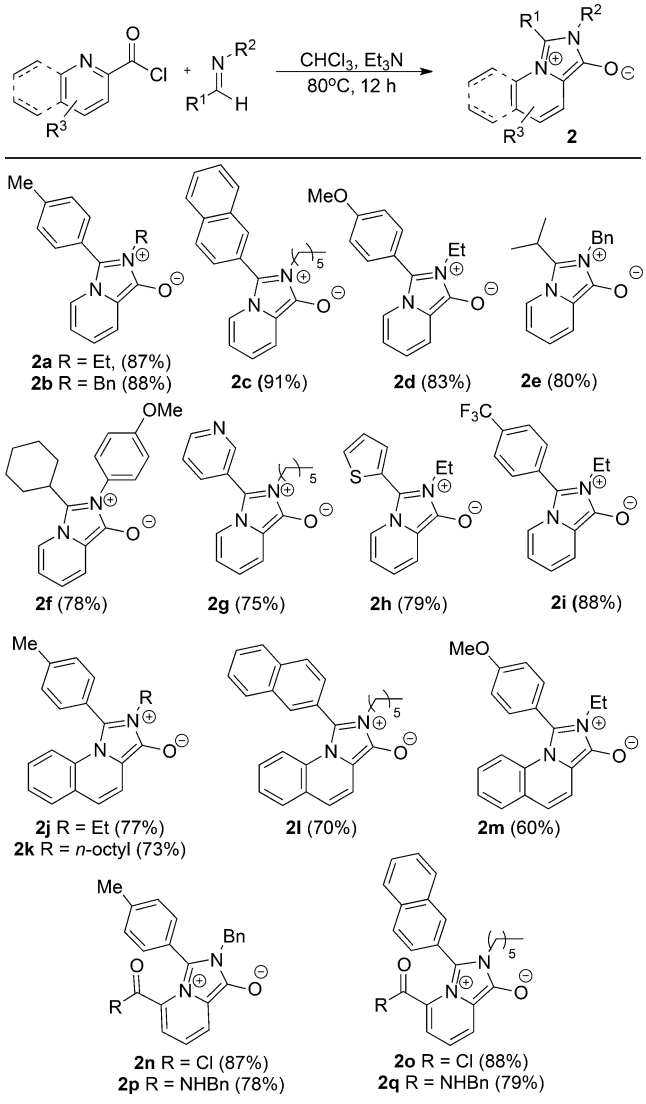
Scheme 2. Synthesis of pyridine-based 1,3-dipole **2a**.

quantitative formation of **2a**. Dipole **2a** can be isolated as a green solid in 87% yield by extraction with toluene. ^{1}H and ^{13}C NMR analysis are consistent with the structure shown, including upfield shifts in the pyridinyl hydrogens (to δ 6.0–7.5 ppm) and carbonyl carbon (δ 150.6 ppm), indicative of delocalization of charge onto the carbonyl oxygen and pyridine (see below).

A feature of **2a** is its generation from available acid chlorides and imines. As such, it is straightforward to prepare a range of new variants of this dipole. Table 1 demonstrates the substrate scope for this transformation. For example, the imine can be systematically varied to incorporate a number of different nitrogen substituents, such as *N*-benzyl (**2b**) or -aromatic (**2f**) units. Similarly, the imine carbon can be modulated to include various substituted aromatics with electron withdrawing (**2i**) or donor (**2d**,**m**) groups. Heteroaromatic substituents are also well tolerated (**2g**,**h**), as are more sensitive enolizable alkyl-substituted imines (**2e**,**f**). The pyridine can be replaced with a diacid chloride (**2n**,**o**), and a quinoline (**2j**–**m**). The former react rapidly with imines (3 h at ambient temperature) and can be further derivatized to access other dipoles (**2p**,**q**). Notably, many of these modifications leads to a significant color change, and can allow the formation of dipoles with colors ranging from red (**2j**–**m**) to blue (**2n**,**o**) to green (**2a**–**i**).[12]

In the case of dipole **2n**, crystals suitable for X-ray structural analysis can be obtained by crystallization from dichloromethane/ pentane. The crystal structure of **2n** is shown in Figure 1, and demonstrates it is indeed a new

Table 1: Substrate scope for 1,3-dipole **2** formation.



[a] Acid chloride (0.3 mmol), imine (0.3 mmol) and Et_3N (90 mg, 0.9 mmol) in 3 mL $CHCl_3$ for 12 h at 80 °C. [b] 3 h at RT. [c] Et_3N (60 mg, 0.6 mmol).

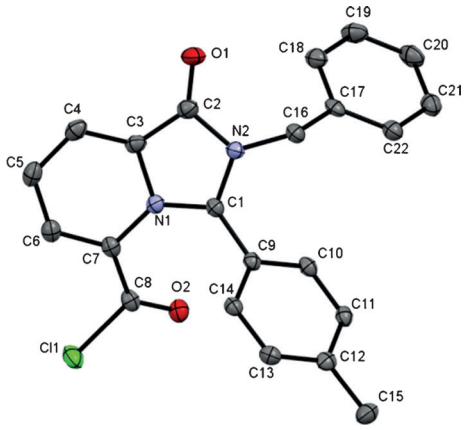
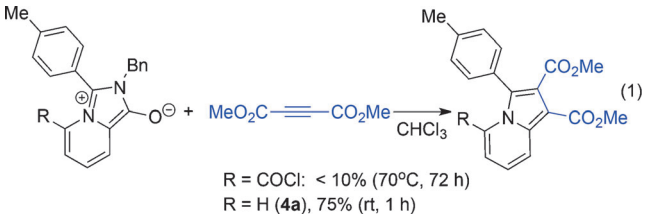


Figure 1. Crystal structure of **2n**. Select bond lengths [Å]: N1–C1 1.343(2), N2–C1 1.376(2), O1–C2 1.228(2), C3–C2 1.428(2), C3–C4 1.370(2), C2–N2 1.402(2), Cl1–C8 1.8035(17), O2–C8 1.197(2).

mesoionic heterocycle.[12] Of note, the N1–C1 (1.343(2) Å) and N2–C1 (1.376(2) Å) bonds in **2n** are close to symmetrical, and intermediate between single and double bonds. In addition, the C2–O1 bond length (1.228(2) Å) is similar to that in typical amides ($PhCONMe_2$, C=O 1.231 Å).[13] This, together with a C2–C3 length between a single and double bond (1.428(2) Å) and upfield pyridinyl ^{1}H NMR resonances, suggests the formal negative charge is likely delocalized throughout the carbonyl and heterocyclic system.

With the ability to form these mesoionic heterocycles in hand, we next questioned if the 1,3-dipole core of **2** can allow their participation in cycloaddition chemistry. For this, it was envisioned that the reduced aromaticity of **2** relative to Besthorn's Red could allow alkyne cycloaddition across the carbon skeleton to be followed by irreversible isocyanate

liberation (which cannot occur with **1**) as a route to build-up indolizines. Initial studies with the crystallographically characterized **2n** show that while it does react sluggishly with the electron poor alkyne dimethylacetylene dicarboxylate (DMAD), it forms indolizine in very low yield [Eq. (1)]. However, removing the electron withdrawing acid chloride functionality on the pyridine (e.g. dipole **2b**), which presumably creates a more nucleophilic dipole, leads to a rapid cycloaddition with the electron poor DMAD within less than 1 h at ambient temperature, and the formation of indolizine **4a** in good yield (75%).

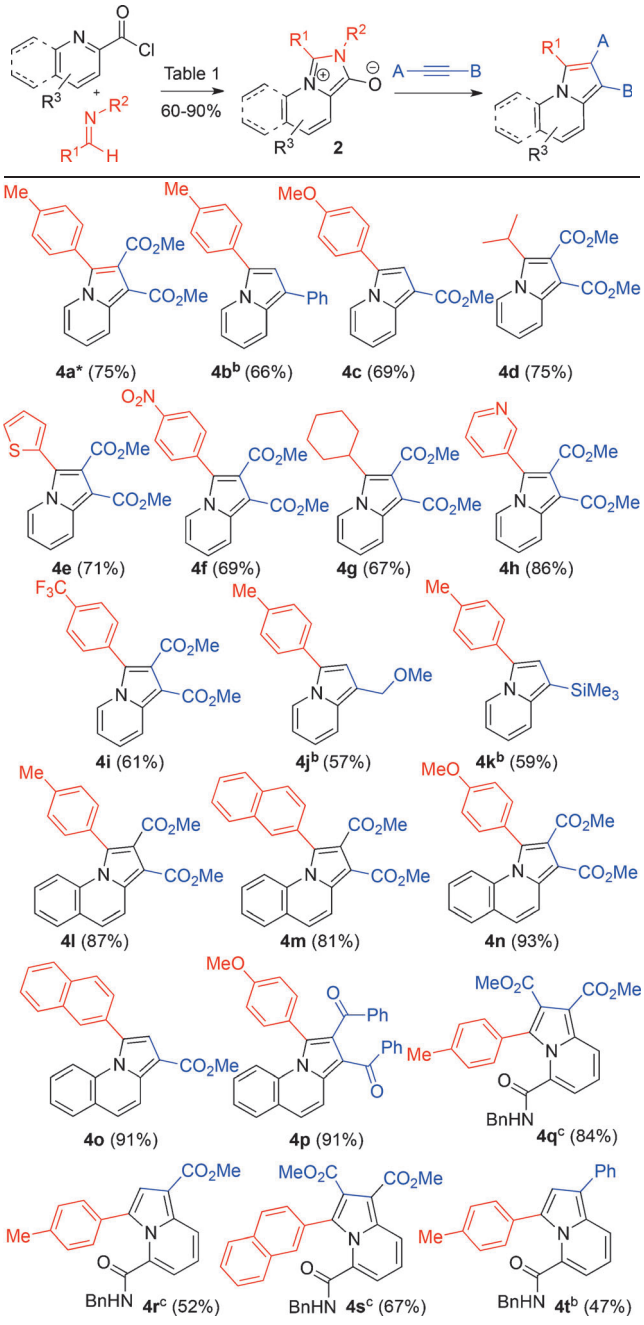


As illustrated in Table 2, the generation of **2** can be coupled with alkyne cycloaddition to create a modular synthesis of indolizines. A range of alkynes can participate in cycloaddition with in situ generated **2**. While electron poor alkynes undergo most rapid reaction (e.g. methyl propiolate, DMAD, and diketoalkynes), mild heating can also allow reactions to proceed with more electron rich alkynes, such as phenylacetylene (**4b**,**t**), those with functional groups (**4j**), and even TMS acetylene (**4k**).[14] In the case of terminal alkynes, only one regioisomeric product is isolated, wherein the alkyne substituent is directed away from the 2-carbon of the imidazolinium core. As this selectivity is consistent with both electron poor and electron rich alkynes, it presumably arises from steric interactions with the R^1 substituent in the imidazolium dipole **2**.

The dipole **2** can also be tuned. In the case of the pyridinyl unit, this can allow the synthesis of various quinoline-based heterocycles (**4l–p**), and functionalized pyridine derivatives (**4q–t**). The cycloaddition reactivity shows a strong dependence upon the electronics of these substituents. While the simple pyridine- and quinoline-derived dipoles react within 30 min at ambient temperature with DMAD, the more electron deficient dipoles **2p** and **2q** require 10 h, and the most electron poor **2o** does not react at all. As with the trends in alkyne substituents, this is consistent with the dipole **2** behaving as the electron-rich component in the cycloaddition reaction, similar to that noted with related *N*-alkylated pyridinium 1,3-dipoles.[15] Finally, the imine unit in **2** can also be modified to tune the 2-substituent in the indolizine. This includes the incorporation of functionalized aromatics with electron donor or withdrawing substituents (**4c**,**i**), alkyl units (**4d**,**g**), and even other heterocycles (**4e**,**h**). Overall combining the formation of **2** with alkyne cycloaddition can provide a novel method to build-up families of indolizines, wherein any of the pyridinyl, imine and alkyne substituents can be systematically modified.

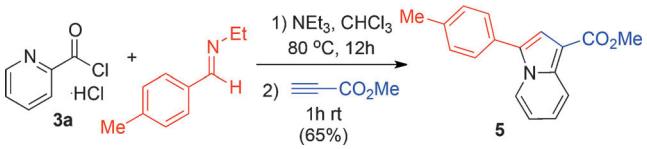
Indolizines are present in a range of pharmaceutically relevant products as well as electronic materials.[11,16] Typical

Table 2: Modular synthesis of indolizines via mesoionic 1,3-dipoles **2**.



[a] **2** formed as in Table 2, alkyne (0.3 mmol) in 2 mL $CHCl_3$, 1 h at ambient temperatue. [b] 65 °C, 24 h. [c] 10 h.

synthetic approaches to these products include cyclizations with synthetic pyridine or pyrrole derivatives,[17–19] substitution on preformed indolizines,[20] or 1,3-dipolar cycloaddition with pyridinium ylides.[21] **2** can be considered a stabilized, mesoionic analogue to these latter 1,3-dipoles, and offers the ability to incorporate a range of aryl, heteroaryl and alkyl units into the 3-indolizine position from simple imines. As an illustration of the utility of this approach, ester-substituted indolizines such as **5** (Scheme 3) has been shown by Lan and You to be strong blue emitting materials of use in fluorescence imaging.[20a] In contrast to its synthesis by substitution



Scheme 3. Targeted syntheses of fluorescent indolizine **5**.

on pre-synthesized indolizines, **5** can be directly generated from **3a**, an imine and an alkyne. In addition to forming **5**, the systematic tuning of each the substrates can in principle allow access to a range of new variants of these products, and from reagents that are either commercially available (e.g. **3a**, alkynes) or easily generated (imines).

In conclusion, a new class of mesoionic, pyridine-based 1,3-dipolar cycloaddition reagent has been developed. These dipoles are stable, easily generated from available substrates, yet can undergo rapid cycloaddition with alkynes to provide a route to synthesize indolizines. Considering the broad variety of dipolar cycloaddition substrates available, as well as the accessibility of **2**, this should provide straightforward access to a range of pyridine-based heterocyclic products. Studies directed towards the latter are in progress.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,3 dipolar cycloaddition · heterocycles · indolizines · mesoionic dipoles · multicomponent reactions

[1] For reviews: a) *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**; b) H.-U. Reissig, R. Zimmer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9708 – 9710; *Angew. Chem.* **2014**, *126*, 9864 – 9866; c) J. Adrio, J. C. Carretero, *Chem. Commun.* **2014**, *50*, 12434 – 12446; d) M. S. Singh, S. Chowdhury, S. Koley, *Tetrahedron* **2016**, *72*, 1603 – 1644.

[2] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004 – 2021; *Angew. Chem.* **2001**, *113*, 2056 – 2075; b) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249 – 1262.

[3] Reviews: a) R. Narayan, M. Potowski, Z. J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296 – 1310; b) E. M. Sletten, C. R. Bertozzi, *Acc. Chem. Res.* **2011**, *44*, 666 – 676; c) J. F. Lutz, Z. Zarafshani, *Adv. Drug Delivery Rev.* **2008**, *60*, 958 – 970; d) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128 – 1137.

[4] For a review: a) G. Delaittre, N. K. Guimard, C. Barner-Kowollik, *Acc. Chem. Res.* **2015**, *48*, 1296 – 1307; For representative examples: b) L. Vretik, H. Ritter, *Macromolecules* **2003**, *36*, 6340 – 6345; c) I.-H. Lee, H. Kim, T.-L. Choi, *J. Am. Chem. Soc.* **2013**, *135*, 3760 – 3763; d) N. V. Handa, S. Li, Jr., A. Gerbec, N. Sumitani, C. J. Hawker, D. Klinger, *J. Am. Chem. Soc.* **2016**, *138*, 6400 – 6403; e) D. C. Leitch, L. V. Kayser, Z. Y. Han, A. R. Siamaki, E. N. Keyzer, A. Gefen, B. A. Arndtsen, *Nat. Commun.* **2015**, *6*, 7411.

[5] Reviews: a) W. Xi, T. F. Scott, C. J. Kloxin, C. N. Bowman, *Adv. Funct. Mater.* **2014**, *24*, 2572 – 2590; b) W. Yan, S. M. Seifermann, P. Pierrat, S. Brase, *Org. Biomol. Chem.* **2015**, *13*, 25 – 54.

[6] R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633 – 645; *Angew. Chem.* **1963**, *75*, 742 – 754.

[7] For an overview of mesoionic heterocycles in cycloaddition: a) G. W. Gribble in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Wiley, Hoboken, **2003**, pp. 681 – 753; For recent reviews, see: b) Münchnones: see Ref. [1b]; c) Sydnones: D. L. Browne, J. P. A. Harrity, *Tetrahedron* **2010**, *66*, 553 – 568; d) Carbenes: R. H. Crabtree, *Coord. Chem. Rev.* **2013**, *257*, 755 – 766; e) Tetrazoles: D. Moderhack, *Heterocycles* **2016**, *92*, 185 – 233.

[8] a) M. S. T. Morin, D. St. -Cyr, B. A. Arndtsen, E. Krenske, K. Houk, *J. Am. Chem. Soc.* **2013**, *135*, 17349; b) M. S. T. Morin, B. A. Arndtsen, *Org. Lett.* **2014**, *16*, 1056; c) D. J. St. -Cyr, M. S. T. Morin, F. Belanger-Gariepy, B. A. Arndtsen, E. Krenske, K. N. Houk, *J. Org. Chem.* **2010**, *75*, 4261.

[9] a) E. Besthorn, G. Jaegle, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 907; b) E. Besthorn, G. Ibele, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 1236.

[10] a) F. Krollpfeiffer, K. Schneider, *Justus Liebigs Ann. Chem.* **1937**, *530*, 34; b) B. R. Brown, E. H. Wild, *J. Chem. Soc.* **1956**, 1158 – 1163.

[11] For reviews: a) V. Sharma, V. Kumar, *Med. Chem. Res.* **2014**, *23*, 3593 – 3606; b) G. S. Singh, E. E. Mmatli, *Eur. J. Med. Chem.* **2011**, *46*, 5237 – 5257; For examples: c) W. B. Han, A. H. Zhang, X. Z. Deng, X. Lei, R. X. Tan, *Org. Lett.* **2016**, *18*, 1816 – 1818.

[12] See the Supporting Information for representative UV/Vis spectra.

[13] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor in *International Tables for Crystallography*, *Vol. C* (Ed.: A. J. C. Wilson), Kluwer, Boston, **1992**, pp. 685 – 706.

[14] The rates of cycloaddition with **2** are comparable to that observed with Münchnones (Ref. [7]), although slower than with unstabilized azomethine ylides, where the formation of the dipole is often rate determining: a) L. M. Harwood, R. J. Vickers in *The Chemistry of Heterocyclic Compounds*, *Vol. 59*A (Eds.: A. Padwa, W. H. Person), Wiley, New York, **2002**, pp. 169 – 252; b) K. Mantelingu, Y. Lin, D. Seidel, *Org. Lett.* **2014**, *16*, 5910 – 5913.

[15] For review: J. Jacobs, E. Van Hende, S. Claessens, N. De Kimpe, *Curr. Org. Chem.* **2011**, *15*, 1340 – 1362.

[16] For review: a) E. Kim, Y. Lee, S. Lee, S. B. Park, *Acc. Chem. Res.* **2015**, *48*, 538 – 547; For representative examples: b) A. J. Huckaba, A. Yella, L. E. McNamara, A. E. Steen, J. S. Murphy, C. A. Carpenter, G. D. Puneky, N. I. Hammer, M. K. Nazeeruddin, M. Grätzel, J. H. Delcamp, *Chem. Eur. J.* **2016**, DOI: 10.1002/chem.201603165; c) T. Mitsumori, M. Bendikov, O. Dautel, F. Wudl, T. Shioya, H. Sato, Y. Sato, *J. Am. Chem. Soc.* **2004**, *126*, 16793 – 16803; d) E. Kim, M. Koh, B. J. Lim, S. B. Park, *J. Am. Chem. Soc.* **2011**, *133*, 6642 – 6649.

[17] For reviews: a) B. Sadowski, J. Klajn, D. T. Gryko, *Org. Biomol. Chem.* **2016**, *14*, 7804 – 7828; b) A. S. Dudnik, V. Gevorgyan in *Catalyzed Carbon-Heteroatom Bond Formation* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2011**, pp. 317 – 410; c) T. Uchida, K. Matsumoto, *Synthesis* **1976**, 209 – 236.

[18] Representative recent examples from substituted pyridines: a) I. V. Seregin, V. Gevorgyan, *J. Am. Chem. Soc.* **2006**, *128*, 12050 – 12051; b) X. Chen, X. Hu, Y. Deng, H. Jiang, W. Zeng, *Org. Lett.* **2016**, *18*, 4742 – 4745; c) B. Zhao, M. Yu, H. Liu, Y. Chen, Y. Yuan, X. Xie, *Adv. Synth. Catal.* **2014**, *356*, 3295 – 3301; d) D. C. Rogness, N. A. Markina, J. P. Waldo, R. C. Larock, *J.*

Org. Chem. **2012**, *77*, 2743 – 2755; e) R. R. Liu, C. J. Lu, M. D. Zhang, J. R. Gao, Y. X. Jia, *Chem. Eur. J.* **2015**, *21*, 7057; f) K. H. Oh, S. M. Kim, Y. Sun, K. Jin, *Org. Lett.* **2016**, *18*, 2204 – 2207; g) J. Barluenga, G. Lonzi, L. Riesgo, L. A. Lopez, M. Tomas, *J. Am. Chem. Soc.* **2010**, *132*, 13200 – 13202; h) M. Gao, J. Tian, A. Lei, *Chem. Asian J.* **2014**, *9*, 2068; i) B. Sahoo, M. N. Hopkinson, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 15545 – 15549; *Angew. Chem.* **2015**, *127*, 15766 – 15770.

[19] Representative recent examples from substituted pyrroles: a) X. Li, X. Sie, Y. Liu, *J. Org. Chem.* **2016**, *81*, 3688 – 3699; b) J. H. Lee, I. Kim, *J. Org. Chem.* **2013**, *78*, 1283 – 1288; c) S. Park, I. Kim, *Tetrahedron* **2015**, *71*, 1982 – 1991; d) V. K. Outlaw, F. B. d-Andrea, C. A. Townsend, *Org. Lett.* **2015**, *17*, 1822 – 1825; e) W. Hao, H. Wang, Q. Ye, W.-X. Zhang, Z. Xi, *Org. Lett.* **2015**, *17*, 5674 – 5677.

[20] For examples: a) B. Liu, Z. Wang, N. Wu, M. Li, J. You, J. Lan, *Chem. Eur. J.* **2012**, *18*, 1599 – 1603; b) B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826 – 1834.

[21] For examples of involving cycloaddition to pyridinium salts, including multicomponent methods: a) J. Day, B. McKeever-Abbas, J. Dowden, *Angew. Chem. Int. Ed.* **2016**, *55*, 5809 – 5813; *Angew. Chem.* **2016**, *128*, 5903 – 5907; b) A. V. Rotaru, I. D. Druta, T. Oeser, T. J. J. Müller, *Helv. Chim. Acta* **2005**, *88*, 1798 – 1812; c) A. R. Katritzky, G. Qiu, B. Yang, H.-Y. He, *J. Org. Chem.* **1999**, *64*, 7618 – 7621; d) U. Bora, A. Saikia, R. C. Boruah, *Org. Lett.* **2003**, *5*, 435 – 438; e) Y. Shang, M. Zhang, S. Yu, K. Ju, X. He, *Tetrahedron Lett.* **2009**, *50*, 6981 – 6984; f) J. Brioche, C. Meyer, J. Cossy, *Org. Lett.* **2015**, *17*, 2800 – 2803; g) F. Li, J. Chen, Y. Hou, Y. Li, X.-Y. Wu, X. Tong, *Org. Lett.* **2015**, *17*, 5376 – 5379; h) M. K. Bayazit, K. S. Coleman, *ARKIVOC* **2014**, *4*, 362 – 371.

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Communications

Mesoionic Dipoles

H. Erguven, D. C. Leitch, E. N. Keyzer, B. A. Arndtsen* ——— ■■■■–■■■■

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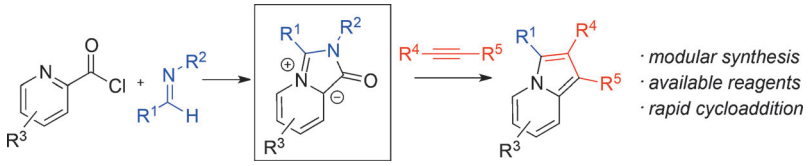

Modular approach: A new class of mesoionic 1,3-dipole has been formed by reaction of pyridinyl-acid chlorides and imines. The modularity of this synthesis can be employed to build-up families of dipoles where every substituent can be modified in one step. Reactivity studies show these dipoles undergo facile 1,3-dipolar cycloaddition with alkynes to form indolizines.

