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Synthesis of 2-Aminoindolizines by 1,3-Dipolar Cycloaddition of Pyridinium Ylides with Electron-Deficient Ynamides

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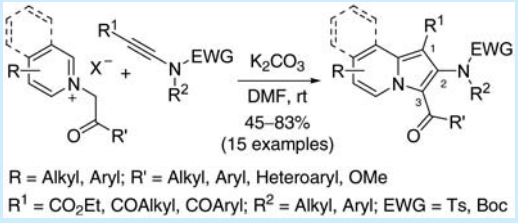
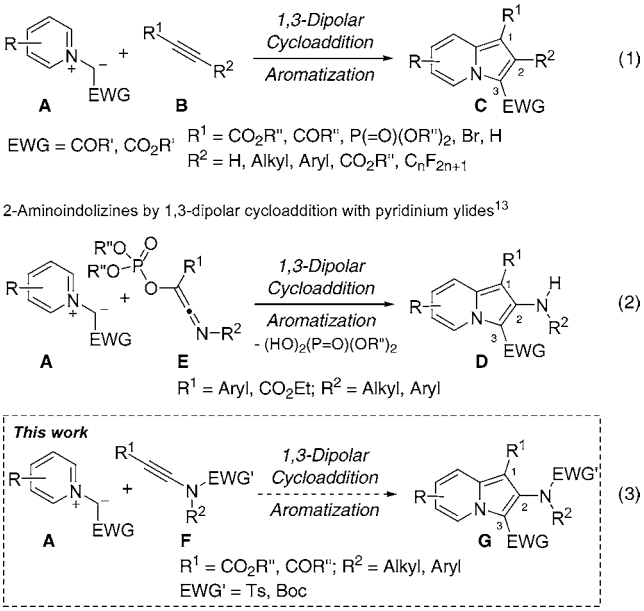
Supporting Information

ABSTRACT: Electron-deficient ynamides, possessing an ynoate or an ynone moiety, have been successfully involved for the first time in a 1,3-dipolar cycloaddition with stabilized pyridinium ylides. These reactions afford an efficient and general access toward a variety of substituted 2-aminoindolizines which can serve as useful precursors for the synthesis of other more complex nitrogen heterocycles.



Because of their diverse biological activities,[1] their photophysical properties,[2] and their use as intermediates in the synthesis of other nitrogen heterocycles,[3] indolizines have elicited considerable interest from researchers.[4−13] The 1,3-dipolar cycloaddition of pyridinium ylides **A**[7] with alkynes **B**, followed by aromatization, affords a convergent and straightforward access toward functionalized indolizines **C**. Acetylenedicarboxylates, ynoates, and ynones have been traditionally employed as dipolarophiles[8] but other suitable partners include perfluoroalkynylphosphonates,[9] bromoalkynes,[10] and some unactivated terminal alkynes[11] (Scheme 1, eq 1). However, all these latter acetylenic dipolarophiles lead to indolizines substituted at C2 by a hydrogen atom or a carbon-containing substituent. 2-Aminoindolizines **D** constitute an interesting subclass of heterosubstituted indolizines, encountered in bioactive compounds or used as scaffolds to access polynitrogen-containing heterocycles.[12] To access 2-aminoindolizines **D** by 1,3-dipolar cycloaddition with pyridinium ylides **A**, *O*-phosphorylated hydroxyketeneimines **E**, generated by Nef isonitrile and Perkow reactions, have previously been employed as partners.[13] In this case, aromatization occurs by loss of the corresponding phosphonic acid (Scheme 1, eq 2). We surmised that a convenient but yet unexplored alternative way to introduce a protected amino group at C2 on indolizines would rely on the use of ynamides **F** as dipolarophiles. In recent years, ynamides have been involved in a wide variety of ring-forming reactions including cycloadditions.[14,15] The nitrogen atom of ynamides can either become part of the newly formed nitrogen heterocycle or be incorporated as an amino substituent onto the created carbo- or heterocycles.[14]

Scheme 1. 1,3-Dipolar Cycloaddition Involving Pyridinium Ylides As a Route to Indolizines



Herein, we report our results on the development of the 1,3-dipolar cycloaddition of pyridinium ylides **A** with electron-deficient ynamides **F**, possessing an ynoate or an ynone moiety, as a general and efficient route toward a variety of substituted 2-aminoindolizines **G** (Scheme 1, eq 3).

The first task was to identify a suitable class of ynamides[16] that would undergo 1,3-dipolar cycloaddition with the ylide generated from pyridinium salt **1a**, which was initially selected as the test substrate (Table 1). In the presence of K_2CO_3 as the base (MeCN, 80 °C), no cycloadduct **5** was observed with phenylethynyl *N*-sulfonylynamide **2** as partner, and the latter compound was almost quantitatively recovered (Table 1, entry 1). This result was not surprising considering that the pyridinium ylide generated from **1a**, and ynamide **2** are both nucleophilic species.[17,18] The poor dipolarophilic activity of compound **2** led us to investigate the reactivity of ynamides possessing an

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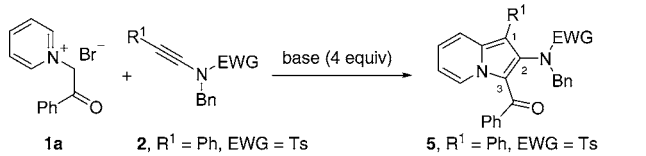
Table 1. 1,3-Dipolar Cycloaddition of Pyridinium Ylide Generated from 1a with Ynamides: Optimization of the Reaction Conditions



1a (2.5 equiv)

2, R^1 = Ph, EWG = Ts
3, R^1 = CO_2Et, EWG = Ts
4, R^1 = CO_2Et, EWG = Boc

5, R^1 = Ph, EWG = Ts
6, R^1 = CO_2Et, EWG = Ts
7, R^1 = CO_2Et, EWG = Boc

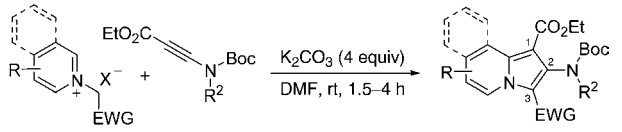
entry	ynamide	base	solvent	time (h)	temp (°C)	product	yield (%)[a]
1	**2**	K_2CO_3	MeCN	5	80	**5**	0
2	**3**	K_2CO_3	MeCN	3	80	**6**	51
3	**3**	K_2CO_3	DMF	2	50	**6**	68
4[b]	**3**	K_2CO_3	DMF	2	50	**6**	50
5	**3**	K2CO$_3$	DMF	4	25	**6**	61
6	**3**	Cs_2CO_3	DMF	4	25	**6**	63
7	**3**	K_3PO_4	DMF	4	25	**6**	46
8	**3**	DBU	DMF	1	25	**6**	15
9	**4**	K_2CO_3	DMF	4	25	**7**	45

[a]Isolated yield. [b]**1a** (1.2 equiv) and K_2CO_3 (2 equiv).

electron-withdrawing substituent on the triple bond. Ynamide **3**, substituted by a carbethoxy group, effectively underwent cycloaddition with the ylide generated from **1a** (2.5 equiv) in the presence of K_2CO_3 (MeCN, 80 °C, 3 h) and directly afforded the desired indolizine **6** in 51% yield (Table 1, entry 2). It is worth noting that no subsequent oxidative treatment was required because the initially generated cycloadduct underwent spontaneous aromatization to provide indolizine **6**. Performing the reaction in DMF at 50 °C significantly improved the yield of **6** (68%) (Table 1, entry 3), but attempts to reduce the quantity of pyridinium salt **1a** (1.2 equiv) led to a less satisfactory result (50%) (Table 1, entry 4). Interestingly, the cycloaddition could be conveniently carried out at room temperature, and in this case, indolizine **6** was isolated in 61% yield (Table 1, entry 5). Among the other inorganic bases screened, the use of Cs_2CO_3 led to a comparable result (63%) (Table 1, entry 6), whereas the yield of **6** decreased slightly (46%) with K_3PO_4 (Table 1, entry 7). Inorganic bases led to better results than DBU (Table 1, entry 8), whose higher solubility in DMF presumably resulted in a too rapid generation of the unstable ylide from pyridinium salt **1a** in the presence of the moderately reactive partner **3**. Thus, K_2CO_3, which is classically used to generate ylides from the corresponding pyridinium salts, was selected as the base for further studies. Interestingly, ynamide **4** in which the nitrogen atom is substituted by a Boc group also underwent 1,3-dipolar cycloaddition and afforded the corresponding indolizine **7** (45%) (Table 1, entry 9). Although the yield of indolizine **6** (61%), in which the nitrogen atom at C2 is substituted by a tosyl group, was higher compared to indolizine **7**, the more readily cleaved *tert*-butyloxy carbamate (Boc) was selected for studying the scope of the 1,3-dipolar cycloaddition of electron-deficient ynamides with pyridinium ylides.[16,19]

The 1,3-dipolar cycloaddition of ynamides incorporating an ynoate moiety was first explored (Table 2). Pyridinium salts derived from α-halo alkyl and heteroaryl ketones (**1b** and **1c**, respectively) or α-halo esters (**1c**–**g**) were used as precursors of the corresponding pyridinium ylides (2.5 equiv) under the previously optimized conditions [K_2CO_3 (4 equiv), DMF, rt]. Efficient cycloaddition took place with ynamides **4**, **8**, and **9** in

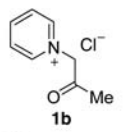
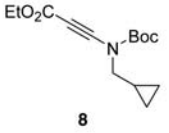
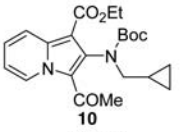
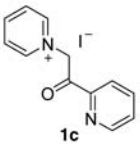
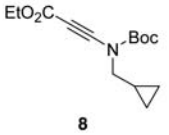
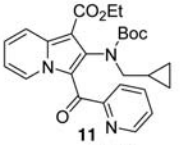
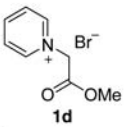
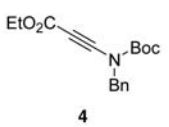
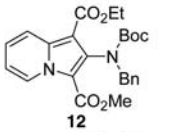
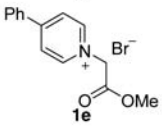
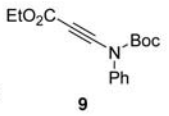
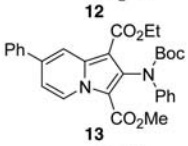
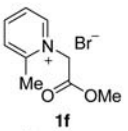
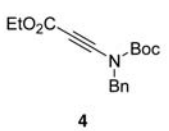
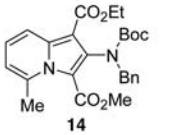
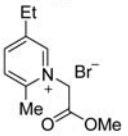
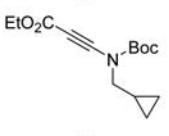
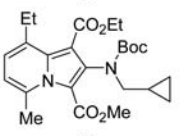
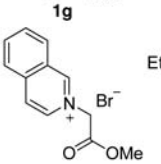
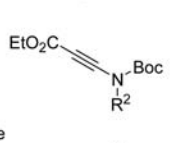
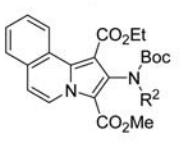
Table 2. 1,3-Dipolar Cycloaddition of Pyridinium Ylides with Ynamides 4, 8, and 9 Incorporating an Ynoate



1b–**1g** (2.5 equiv)
1h (5 equiv)

4, **8**, **9**

10–**17**

entry	pyridinium salt	ynamide	product	yield (%)[a]
1	 **1b**	 **8**	 **10**	70
2	 **1c**	 **8**	 **11**	65
3	 **1d**	 **4**	 **12**	68
4	 **1e**	 **9**	 **13**	70
5	 **1f**	 **4**	 **14**	65
6	 **1g**	 **8**	 **15**	52
7	 **1h**	 **4**, R^2 = Bn	 **16**, R^2 = Bn	56[b]
8	**1h**	**9**, R^2 = Ph	**17**, R^2 = Ph	74[c]

[a]Isolated yield. [b]Reaction time 36 h. [c]Reaction run at 50 °C, 6 h.

which the nitrogen atom is substituted by a benzyl, a cyclopropylmethyl, or a phenyl group, respectively. The corresponding 2-aminoindolizines **10**–**15** were isolated in moderate to good yields (52–70%) (Table 2, entries 1–6). It is worth mentioning that the substitution pattern of the pyridinium salts **1e**–**g** was selected purposely to avoid the formation of regioisomers. As anticipated, for unsymmetrical pyridinium salts **1f** and **1g**, the 1,3-dipolar cycloaddition occurred at the less substituted carbon of the pyridinium ring (Table 2, entries 5 and 6).

The ylide generated from isoquinolinium salt **1h** was also a suitable partner for the cycloaddition with ynamides **4** and **9**, which led to the corresponding pyrroloisoquinolines **16** (56%) and **17** (74%), respectively. Nevertheless, a large excess of the salt **1h** (5 equiv) was required in both cases to achieve full conversion as well as a longer reaction time (36 h) for the formation of **16**

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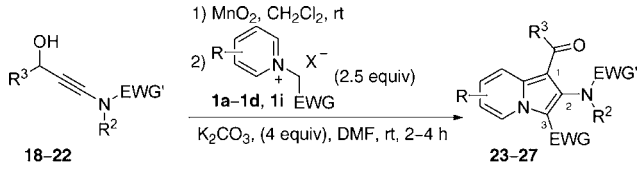
(Table 2, entry 7) or a higher temperature (50 °C) to obtain **17** (Table 2, entry 8).[20]

The 1,3-dipolar cycloaddition was then investigated with ynamides incorporating an ynone moiety, which were conveniently generated by oxidation of the corresponding ynamides **18**−**22** possessing a propargylic alcohol and used without further purification (Table 3).[21]

Table 3. 1,3-Dipolar Cycloaddition of Pyridinium Ylides with Ynamides 18′−22′ Incorporating an Ynone (Generated from Alcohols 18−22)



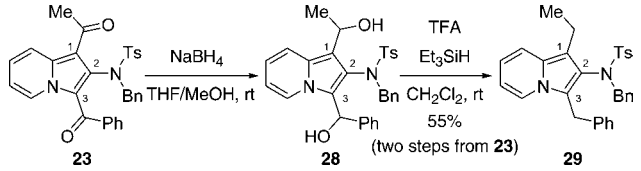
entry	pyridinium salt	ynamide	product	yield (%)[a]
1	**1a**	**18′**	**23**	53
2	**1b**	**19′**	**24**	83
3	**1c**	**20′**	**25**	55
4	**1i**	**21′**	**26**	45
5	**1i**	**22′**	**27**	56

[a]Isolated overall yield (two steps from the corresponding ynamido alcohol).

The 1,3-dipolar cycloaddition of ynamido ketones **18′**−**22′** with ylides derived from pyridinium salts **1a**−**1c** and **1i** delivered the corresponding indolizines **23**−**27** in moderate to high overall yields (45−83%, two steps from ynamido-alcohols **18**−**22**). The scope is rather broad as a variety of 2-aminoindolizines incorporating either a methyl ketone (Table 3, entry 1), an aryl ketone (Table 3, entry 2) or a substituted alkyl ketone (Table 3, entries 3−5) at C1 can be readily obtained by this sequence.

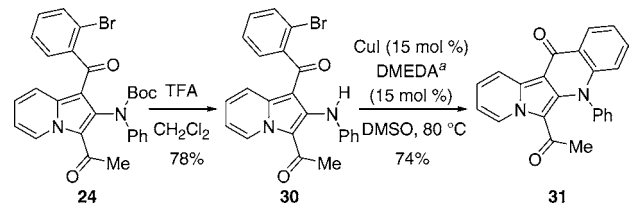
The highly functionalized 2-aminoindolizines **G**, arising from the 1,3-dipolar cycloaddition of stabilized pyridinium ylides **A** with electron-deficient ynamides **F** invariably contain carbonyl groups at C1 and C3. However, it is possible to take advantage of the electron-rich pyrrole nucleus to access 2-aminoindolizines substituted by alkyl chains at C1 and C3. Thus, reduction of both ketones in compound **23** with $NaBH_4$ led to the corresponding diol **28** which underwent double deoxygenation by reduction with Et_3SiH in the presence of TFA (CH_2Cl_2, rt). This sequence afforded indolizine **29** (55%) substituted by an ethyl group at C1 and a benzyl group at C3, a compound that would formally result from the 1,3-dipolar cycloaddition between an unstabilized pyridinium ylide and an unactivated ynamide which cannot be achieved under the same conditions (Scheme 2).

Scheme 2. Synthesis of a 2-Aminoindolizine 29 with Alkyl Groups at C1 and C3



To illustrate that functionalized 2-aminoindolizines **G** can serve as useful building blocks for the elaboration of more complex heterocyclic compounds, the synthesis of the indolizinoquinolinone **31**, which incorporates a scaffold of interest in medicinal chemistry,[22] was achieved from cycloadduct **24**. The Boc group was easily cleaved (TFA, CH_2Cl_2), and the resulting *N*-phenylheteroarylamine **30** (78%) was engaged in a copper-catalyzed intramolecular amination[23] which enabled the efficient construction of the quinolone part of the indolizinoquinolinone **31** (74%) (Scheme 3).

Scheme 3. Synthesis of Indoloquinolizidine 31 by Intramolecular Copper-Catalyzed Amination



[a]DMEDA = $MeNH(CH_2)_2NHMe$.

In conclusion, we have demonstrated that the 1,3-dipolar cycloaddition of stabilized pyridinium ylides with electron-deficient ynamides, activated by an ester or a ketone, provides a straightforward and convenient access to highly functionalized 2-aminoindolizines. These results contribute to expand the repertoire of the cycloaddition reactions in which ynamides can be successfully involved to produce heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01205.

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Notes

The authors declare no competing financial interest.

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