Reactions of Heterocyclic Ketene Aminals with 2-[3-Oxoisobenzofuran-1(3*H*)-ylidene]malononitrile: Synthesis of Novel Polyfunctionalized 1,4-Dihydropyridine-Fused 1,3-Diazaheterocycles

Wen-Yuan Xu,[a,b] Yue-Mei Jia,[b] Jing-Kui Yang,*[a] Zhi-Tang Huang,*[b] Chu-Yi Yu*[b]

[a] College of Chemistry and Chemical Engineering, Graduate University of Chinese Academy of Sciences, Beijing 100049, P. R. of China

[b] Beijing National Laboratory for Molecular Science (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, P. R. of China
Fax +86(10)82616433; E-mail: yucy@iccas.ac.cn

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Abstract: An efficient method has been developed for the synthesis of a novel kind of polyfunctionalized 1,4-dihydropyridine-fused 1,3-diazaheterocycles via the reactions of heterocyclic ketene aminals (HKAs) with 2-[3-oxoisobenzofuran-1(3*H*)-ylidene]malononitrile.

Key words: heterocyclic ketene aminals, polyfunctionalized, 1,4-dihydropyridine-fused 1,3-diazaheterocycles, synthesis

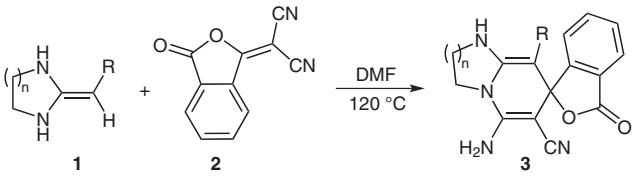
Heterocyclic ketene aminals (HKAs), also known as cyclic 1,1-enediamines, are versatile starting materials for the syntheses of a wide variety of heterocycles.[1,2] Since both the α-carbon and the secondary amino group in ketene aminals could be involved in the reactions with electrophiles, HKAs have been used as bisnucleophiles to construct fused azaheterocycles.[3–6] Furthermore, some HKAs and their derivatives might be used as pesticides,[7] antibacterial agents,[8] antianxiety agents,[9] antileishmanial agents[10] and anticancer agents.[11]

Spiro compounds are of recent interest due to their many uses in material sciences[12] and asymmetrical catalysis[13] and their prevalence in naturally occurring molecules.[14,15] Therefore, the syntheses of spiro compounds have been of intensive interest in recent years.[16]

1,4-Dihydropyridines are kinds of important compounds that have wide uses as pharmaceuticals[17,18] and synthetic intermediates.[19] The construction of multisubstituted dihydropyridines has attracted considerable attention in synthetic organic chemistry since Hantzsch's pioneering work more than one century ago.[20]

In the context of our continuing efforts in diversity-oriented synthesis of 1,4-dihydropyridine-fused 1,3-diazaheterocycles, we envisaged that it could be possible to develop a simple and novel method to construct the highly functionalized 1,4-dihydropyridine-fused 1,3-diazaheterocycles **3** via the reaction of HKAs **1** and 2-[3-oxoisobenzofuran-1(3*H*)-ylidene]malononitrile (**2**).[21] Compound **2** is an ideal exocyclic double-bond compound for the synthesis of spiro compounds as it possesses versatile functionalities, which makes it a good biselectrophilic reagent to construct the titled compounds with bisnucleophilic HKAs **1**.

As was expected, HKAs **1** reacted with 2-[3-oxoisobenzofuran-1(3*H*)-ylidene]malononitrile **2** smoothly to afford the novel structures of polyfunctionalized 1,4-dihydropyridine-fused 1,3-diazaheterocycles **3**, i.e. spiro(imidazo[1,2-*a*]pyridine-7,1′-isobenzofuran)-6′-carbonitriles and spiro(isobenzofuran-1,8′-pyrido[1,2-*a*]pyrimidine)-7′-carbonitriles (Scheme 1).[22]



n = 1, 2; R = CN, NO_2, CO_2Et, 4-XPh-CO; X = H, Me, OMe, Cl, Br, F, Ph

Scheme 1 Reactions of HKAs with 2-[3-oxoisobenzofuran-1(3*H*)-ylidene]malononitrile

2-[3-Oxoisobenzofuran-1(3*H*)-ylidene]malononitrile (**2**), prepared according to the literature,[21a] was stirred with HKAs **1** in *N*,*N*-dimethylformamide at 120 °C to give **3** (Table 1). Most of the reactions proceeded well and resulted in the formation of the desired products in excellent yields. The relatively lower yield of **3b**, **3f** and **3n** was ascribed to the partial decomposition of the final products upon workup. It is noteworthy that compounds **3** were formed at temperatures over 120 °C, but deteriorated at temperature above 130 °C under the same reaction conditions. Therefore, the reactions should be conducted at around 120 °C.

The structures of compounds **3a–o** were determined by spectroscopic data and high-resolution mass spectroscopy. IR, ^{1}H NMR and ^{13}C NMR indicated that **3a–o** were highly substituted with a number of functional groups, including two amino groups, a cyano group, and a lactone substructure. The absorption in IR at about 3300, 2190–2224 and 1630–1651 cm^{-1} indicated the existence of amino, cyano and carbonyl groups. Furthermore, for some products, a signal appeared at δ = 10.77–8.90 ppm in ^{1}H NMR, which was attributed to the amino group, which in turn was ascribed to the intramolecular hydrogen bond be-

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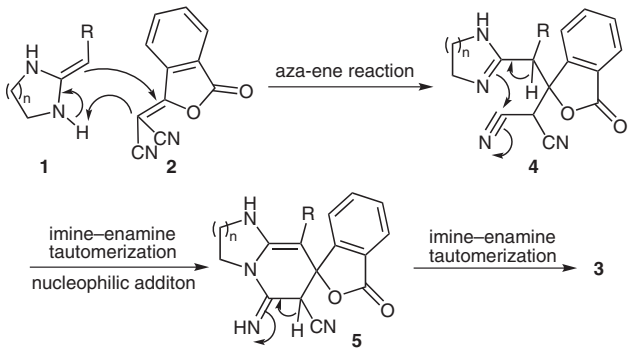
Table 1 Synthesis of 1,4-Dihydropyridine-Fused 1,3-Diazaheterocycles **3**

Entry	HKA **1**	R	Solvent	Temp (°C)	n	Product	Yield (%)[a]
1	**1a**	PhC=O	DMF	120	1	**3a**	95
2	**1b**	4-MeC_6H_4C=O	DMF	120	1	**3b**	89
3	**1c**	4-$MeOC_6H_4C$=O	DMF	120	1	**3c**	96
4	**1d**	4-ClC_6H_4C=O	DMF	120	1	**3d**	90
5	**1e**	4-FC_6H_4C=O	DMF	120	1	**3e**	91
6	**1f**	4-PhC_6H_4C=O	DMF	120	1	**3f**	87
7	**1g**	NO_2	DMF	120	1	**3g**	98
8	**1h**	CN	DMF	120	1	**3h**	98
9	**1i**	CO_2Et	DMF	120	1	**3i**	99
10	**1j**	NO_2	DMF	120	2	**3j**	99
11	**1k**	PhC=O	DMF	120	2	**3k**	95
12	**1l**	4-MeC_6H_4C=O	DMF	120	2	**3l**	90
13	**1m**	4-$MeOC_6H_4C$=O	DMF	120	2	**3m**	96
14	**1n**	4-ClC_6H_4C=O	DMF	120	2	**3n**	88
15	**1o**	4-BrC_6H_4C=O	DMF	120	2	**3o**	94

[a] Isolated yield.

tween amino and benzoyl carbonyl group.[23] The α-H and one of NH signals related with **1a–o** disappeared in final products **3a–o** as shown by ^{1}H NMR. One of the cyano groups in compound **2** disappeared and only one cyano signal (δ = 115.5–117.8 ppm) remained in the final products **3a–o** as shown by ^{13}C NMR, except for **3h** which had another cyano group derived from substrate **1h**. A pair of downfield shift signals (δ = 150.1–155.9 ppm) and another pair of upfield shift signals (δ = 77–89.8 ppm) indicated that this pair of double bonds was highly polarized, which further proved the product's structures.

A plausible mechanism of the reaction is depicted in Scheme 2. The reaction proceeds in a cascade way. Firstly, the ene-component HKAs **1** and the enophile 2-[3-oxoisobenzofuran-1(3*H*)-ylidene]malononitrile (**2**) undergo an aza-ene reaction to give the intermediate **4**, which undergoes successive imine-enamine tautomerization, followed by nucleophilic addition of the secondary amino group to the cyano group, resulting in the formation of intermediate **5**. Consecutive 1,3-H migration or imine-enamine tautomerization gives the relatively more stable dihydropyridines **3**.



Scheme 2 Mechanism of the formation of 1,4-dihydropyridine-fused 1,3-diazaheterocycles **3**

In conclusion, a simple and easy method has been developed for the quick construction of a novel kind of polyfunctionalized 1,4-dihydropyridine-fused 1,3-diazaheterocycles by the reaction of HKAs **1** with 2-[3-oxoisobenzofuran-1(3*H*)-ylidene]malononitrile (**2**). These types of heterocycles contain a number of functional groups and are therefore valuable precursors for diversity-oriented synthesis of pyridine-fused 1,3-diazaheterocycles libraries, which are of potential uses in the facile preparation of biologically active molecules. Further work on the reactions of compounds **3** and **5** is under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(22) **General Procedure for the Synthesis of 3**: Heterocyclic ketene aminals **1** (1 mmol) and 2-[3-oxoisobenzofuran-1(3*H*)-ylidene]malononitrile (**2**; 1 mmol) were stirred in DMF (5 mL) at 120 °C until the reaction was complete as monitored by TLC (ca. 2–12 h). After the reaction mixture was cooled to r.t., the solvents were removed in vacuo and the resulting solids were subjected to recrystallization (MeOH–Et_2O or MeCN) to provide the desired fused heterospiro compounds **3**.
Compound **3f**: yellow solid; mp 306–307 °C. IR (KBr): 3363 (m), 3331 (m), 2211 (m), 1633 (s), 1603 (s), 1582 (s), 1558 (s), 1508 (m), 1370 (s), 1311 (s), 931 (m), 849 (w), 763 (m), 732 (m), 678 (m), 652 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.73 (d, *J* = 7.5 Hz, 1 H), 7.53–7.63 (m, 4 H), 7.44–7.47 (m, 4 H), 7.30–7.40 (m, 2 H), 7.20–7.25 (m, 1 H), 7.04 (d, *J* = 7.2 Hz, 1 H), 4.03–4.22 (m, 2 H), 3.79–3.94 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 192.0, 166.8, 154.4, 152.7, 142.9, 139.2, 137.7, 132.5, 137.0, 130.6, 130.2, 129.5, 129.1, 128.9, 128.3, 128.0, 126.7, 125.8, 117.1, 105.1, 77.9, 48.6, 45.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{21}N_4O_3^+$: 461.1608; found: 461.1609.
Compound **3o**: yellow solid; mp 205–207 °C. IR (KBr): 3282 (m), 3061 (m), 2212 (m), 1631 (s), 1604 (s), 1560 (s), 1528 (s), 1480 (m), 1376 (s), 1337 (s), 1280 (m), 1068 (m), 927 (m), 850 (m), 776 (m), 676 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.63 (d, *J* = 6.9 Hz, 1 H), 7.17–7.31 (m, 6 H), 7.00 (d, *J* = 6.6 Hz, 1 H), 4.01–4.02 (m, 2 H), 3.40–3.42 (m, 2 H), 2.00–2.03 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 192.7, 166.8, 156.1, 154.5, 152.1, 139.7, 137.2, 132.4, 130.6, 130.2, 130.1, 129.9, 128.5, 124.2, 117.2, 103.2, 83.5, 48.6, 42.8, 18.6. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}N_4O_3Br^+$: 477.0571; found: 477.0562.

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