Check for updates

View Article Online
View Journal

Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: D. P. Chauhan, S. J. J. Varma, M. Gudem, N. Panigrahi, K. Singh, A. Hazra and P. Talukdar, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB00499K.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB00499K

Journal Name

ARTICLE

Intramolecular cascade rearrangements of enynamine derived ketenimines: Access to acyclic and cyclic amidines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

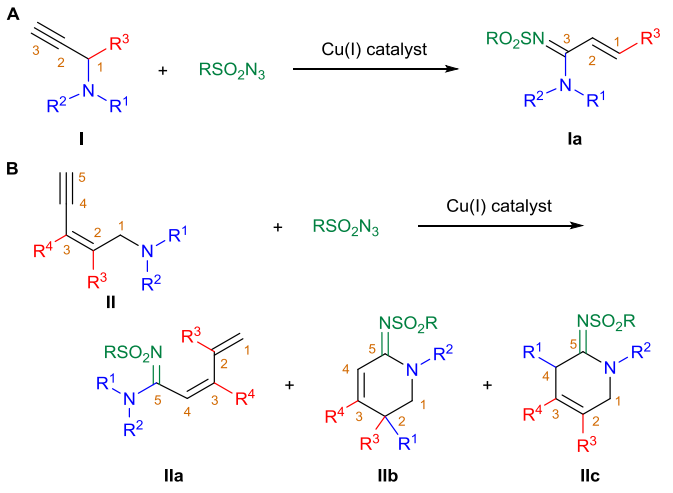
Dinesh Pratapsinh Chauhan,[a] Sreejith J. Varma,[a,b] Mahesh Gudem,[a] Nihar Panigrahi,[a] Khushboo Singh,[a,c] Anirban Hazra,[a] and Pinaki Talukdar*[a]

Copper-catalyzed reaction of enynamines with sulfonylazides provides acyclic and cyclic amidines. Nucleophilic addition of the tethered amino group on the *in situ* generated ketenimine forms a six-membered cyclic zwitterionic intermediate which facilitates migration of the tethered amino group to the C_5-center giving the acyclic amidine. On the other hand, migration of a substituent on the amino group to C_2- and C_4-centers results in the formation of cyclic amidines. Computational studies were carried out to validate the mechanism which indicate that the product distribution of the process depends on the substitutions on the enynamine backbone.

Introduction

Since the dawn of modern chemistry, reactive intermediates have served as an inspiration for the development of new reactions, molecules, and materials. Indeed, the strategies involving reactive intermediates have made possible the construction of numerous complex organic frameworks in easier and shorter routes. In general, reactive intermediates readily undergo chemical transformations, and their reactions are typically exothermic.[1] Among several reactive entities in organic chemistry, ketenimines represent an important class of reactive intermediates which has been applied widely as a powerful synthon. During last two decades, several methodologies were developed towards the formation of ketenimine, and to explore its synthetic applications.[2] Because of the remarkable reactivity, the ketenimine was comprehensively applied in the synthesis of many complex compounds.[3] Interception of this reactive species with other functional groups led to novel strategies for the reaction discovery.[4] Going through literature, it is observed that ketenimine undergoes nucleophilic addition,[2i] cycloaddition,[5] radical addition,[6] electrocyclic ring-closure reactions,[7] and σ rearrangements.[3b,3c,8] For example, *N*-sulfonyl/phosphoryl ketenimine undergoes addition reactions with external nucleophiles *e.g.* amines, alcohols, pyrroles, indoles, ammonium salts, etc.[2i]

In 2014, we reported a novel rearrangement of ketenimine intermediate, generated from the substituted propargylamine **I**, by an internal amine nucleophile forming amidine **Ia** via the [1,3]-amino group migration (Scheme 1A).[9] Our success in this area prompted us to investigate the possibilities of new rearrangement reactions of ketenimine, envisaged through the incorporation of an additional alkene moiety at the C_2-C_3 position. Here, we report that such structural modification leads to not only the formation of acyclic amidine **IIa** but also allows the access to highly functionalized cyclic amidines **IIb** and **IIc** from **II** (Scheme 1B).



Scheme 1. Reaction of propargylamine **I** with sulfonylazide under Cu(I) catalyzed conditions giving amidine **Ia** as the [1,3]-amino group migration product (**A**). Reaction enynamine **II** with sulfonylazide under Cu(I) catalyzed conditions in the formation of acyclic and cyclic amidines **IIa-IIc** (**B**).

[a] Department of Chemistry, Indian Institute of Science Education and Research Pune, Dr. Homi Bhabha Road, Pashan, Pune 411008, Maharashtra, India.
Email: ptalukdar@iiserpune.ac.in
[b] *Present address: Institut de Science et d'Ingénierie Supramoléculaires (ISIS), Université de Strasbourg, 8 allée Gaspard Monge BP 70028 F-67000, Strasbourg Cedex, France.*
[c] *Present address: Department of Chemistry, University of Massachusetts Amherst, Amherst, Massachusetts 01003, United States.*
† We gratefully acknowledge SERB, Govt. of India (EMR/2014/000873B) for funding our work. DPC thanks CSIR, Govt. of India for research fellowship.
‡ Electronic Supplementary Information (ESI) available: Synthetic procedures and experimental methods, additional experimental details and NMR spectra. See DOI: 10.1039/x0xx00000x

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB00499K

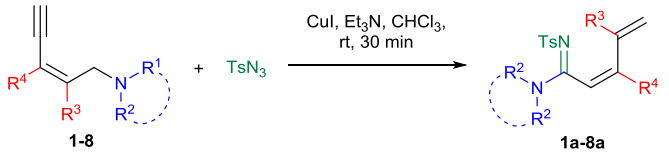
Results and discussion

We started our preliminary investigation with the conjugated enynamine substrate **1**, where the amino moiety is the 4-morpholinyl group. The reaction of **1** with TsN_3 (1.1 equiv) in presence of catalytic CuI (10 mol%) and Et_3N (1.5 equiv) in $CHCl_3$ provided the [1,5]-amino group migration product **1a** in 67% yield (Table 1, Entry 1). When substrates **2-4** were used by introducing phenyl group at either C_2- or C_3- or both positions, corresponding [1,5]-amino group migration products **2a-4a** were formed (Entries 2-4). The observations were comparable when enynamine substrates were decorated with acyclic amino groups, and C_2- and C_3-positions were also randomly substituted with a phenyl group (Entries 5-8).

An interesting twist in the product formation was observed when the enyne was decorated with the -NBn_2 group. Such a substrate **9** with $R^3 = R^4 = H$ when reacted with TsN_3 under the CuI catalytic conditions, cyclic amidines **9b** (51%) and **9c** (16%) were formed apart from the expected acyclic amidine **9a** (23%) (Table 2, entry 1). The general plausible mechanism of the process is depicted in Scheme 2. Reaction of enynamine **II** with a sulfonylazide under Cu(I) catalytic conditions provides the triazole intermediate **IId** which upon releasing a N_2 molecule gives ketenimine **IIe**.[10] Capture of **IIe** by the internal amino group leads to the 6-*exo-dig* cyclization[11] to form the zwitterionic intermediate **IIf** which has canonical forms **IIg** and **IIh**. The C_1–N bond cleavage of the cyclic intermediate **IIf** via E1cB process leads to the formation of [1,5]-amino group migration product **IIa**. The electrophilic migration of the R_1 group of the intermediate **IIf** to its C_2-center gives the cyclic amidine **IIb**. On the other hand, an electrophilic migration of the R_1 group to the C_4-center facilitates the formation of adduct **IIc**.

We further investigated the effects of R and R^1–R^4 groups on product distribution to obtain greater insight on observed rearrangement processes. All conjugated enynamine substrates were prepared according to three general sequences outlined in Schemes S1, S3, S5 and S7.[12] The -NBn_2 substituted enynamine **10** (R^3 = Ph, R^4 = H), when treated with TsN_3, cyclic amidines **10b** (50%) and **10c** (40%) were

Table 1. Formation of [1,5]-amino group migration products from enynamines.

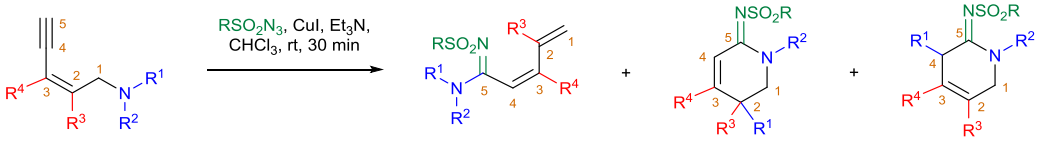


1-8 1a-8a

Entry	1-8	-NR^1R^2	R^3	R^4	1a-8a (Yield)[a]
1	**1**	-(4-morpholinyl)	H	H	**1a** (67%)
2	**2**	-(4-morpholinyl)	Ph	H	**2a** (76%)
3	**3**	-(4-morpholinyl)	H	Ph	**3a** (70%)
4	**4**	-(4-morpholinyl)	Ph	Ph	**4a** (65%)
5	**5**	-$N(Et)_2$	H	Ph	**5a** (67%)
6	**6**	-$N(^iPr)_2$	H	H	**6a** (57%)
7	**7**	-$N(^nHex)_2$	H	H	**7a** (62%)
8	**8**	-$N(^nHex)_2$	H	Ph	**8a** (62%)

[a]All yields are isolated yields.

Table 2. Scope of Cu(I) catalyzed reaction of enynamine and sulfonylazide.



9-24 9a-26a 9b-26b 9c-26c

Entry	9-24	R	R^1	R^2	R^3	R^4	9a-26a (Yield)[a]	9b-26b (Yield)[a]	9c-26c (Yield)[a]
1	**9**	4-*Me*C_6H_4	Bn[b]	Bn	H	H	**9a** (23%)	**9b** (51%)	**9c** (16%)
2	**10**	4-*Me*C_6H_4	Bn	Bn	Ph	H	**10a** (0%)	**10b** (50%)	**10c** (40%)
3	**11**	4-*Me*C_6H_4	Bn	Bn	H	Ph	**11a** (84%)	**11b** (5%)	**11c** (0%)
4	**12**	4-*Me*C_6H_4	Bn	Bn	Ph	Ph	**12a** (48%)	**12b** (30%)	**12c** (0%)
5	**13**	4-*Me*C_6H_4	4-*CN*Bn[c]	4-*CN*Bn	H	H	**13a** (13%)	**13b** (37%)	**13c** (23%)
6	**14**	4-*Me*C_6H_4	4-*CN*Bn	4-*CN*Bn	Ph	H	**14a** (0%)	**14b** (51%)	**14c** (32%)
7	**15**	4-*Me*C_6H_4	4-*CN*Bn	4-*CN*Bn	H	Ph	**15a** (77%)	**15b** (0%)	**15c** (0%)
8	**16**	4-*Me*C_6H_4	4-*CN*Bn	4-*CN*Bn	Ph	Ph	**16a** (73%)	**16b** (18%)	**16c** (0%)
9	**17**	4-*Me*C_6H_4	4-*MeO*Bn[d]	4-*MeO*Bn	H	H	**17a** (0%)	**17b** (63%)	**17c** (12%)
10	**18**	4-*Me*C_6H_4	4-*MeO*Bn	4-*MeO*Bn	Ph	H	**18a** (0%)	**18b** (60%)	**18c** (11%)
11	**19**	4-*Me*C_6H_4	4-*MeO*Bn	4-*MeO*Bn	H	Ph	**19a** (8%)	**19b** (70%)	**19c** (6%)
12	**20**	4-*Me*C_6H_4	4-*MeO*Bn	4-*MeO*Bn	Ph	Ph	**20a** (0%)	**20b** (68%)	**20c** (0%)
13	**21**	4-*Me*C_6H_4	Bn	4-*CN*Bn	H	H	**21a** (14%)	**21b** (39%)	**21c** (23%)
14	**22**	4-*Me*C_6H_4	Bn	4-*CN*Bn	Ph	H	**22a** (0%)	**22b** (50%)	**22c** (25%)
15	**23**	4-*Me*C_6H_4	Bn	4-*CN*Bn	H	Ph	**23a** (86%)	**23b** (0%)	**23c** (0%)
16	**24**	4-*Me*C_6H_4	Bn	4-*CN*Bn	Ph	Ph	**24a** (46%)	**24b** (29%)	**24c** (0%)
17	**10**	Me	Bn	Bn	Ph	H	**25a** (0%)	**25b** (52%)	**25c** (34%)
18	**11**	4-$NO_2C_6H_4$	Bn	Bn	H	Ph	**26a** (49%)	**26b** (25%)	**26c** (0%)

[a]All yields are isolated yields. [b]Bn = Benzyl, [c]4-*CN*Bn = 4-cyanobenzyl, [d]4-*MeO*Bn = 4-methoxybenzyl.

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

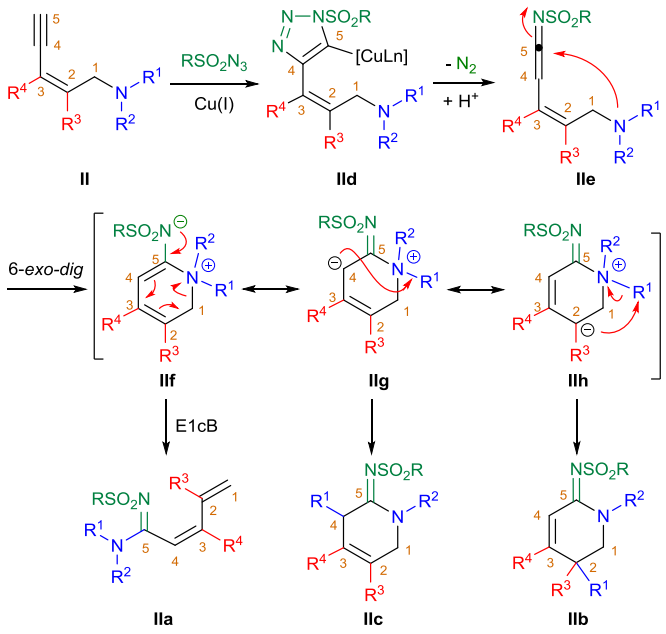
Organic & Biomolecular Chemistry Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

View Article Online
DOI: 10.1039/C7OB00499K

Journal Name

ARTICLE



Scheme 2. Proposed general mechanism for the formation of **IIa**, **IIb** and **IIc** from **II**.

obtained as rearranged products (Entry 2). Corresponding acyclic amidine **10a** could not be traced from the reaction mixture. On the contrary, the substrate **11** (R^3 = H, R^4 = Ph) under similar reaction conditions provided **11a** (84%) as the major isomer (Entry 3). In this case, the isomer **11b** was isolated as the minor product, and formation of **11c** could not be detected. Similar reaction of **12** (R^3 = R^4 = Ph) gave two products **12a** (48%) and **12b** (30%) (Entry 4). Apart from one dimensional ^{1}H and ^{13}C NMR studies, the molecular structures acyclic and cyclic amidines were further confirmed using either single crystal X-ray diffraction (*e.g.* Fig. 1 for **10b** and **11a**) or two-dimensional NMR spectroscopic (*e.g.* ^{1}H-^{1}H COSY and ^{1}H-^{13}C HETCOR for **9c**, **21c** and **25c**) analysis (see ESI).

Quantum chemical calculations were done to validate the proposed mechanism and rationalize the product distribution. For a simplified version of enynamine **III** with R^1 = R^2 = Me, R^3 = R^4 = H (Fig. S7), optimized structures of the cyclic intermediate **IIIf** (Fig. 2), and corresponding products **IIIa**, **IIIb**, and **IIIc** were obtained using the MP2 and DFT (B3LYP) methods with the 6-31G basis set (Fig. S7). Transition state structures **IIIa'**, **IIIb'** and **IIIc'** corresponding to these products (Fig. 2), and the reaction barrier of each process were also obtained (Table S1). Small differences in the barrier heights between MP2 and DFT for a given product were observed. The MP2 method is known to be more reliable than DFT (B3LYP) for calculating reaction barriers,[13] but the former is computationally more expensive than the latter.

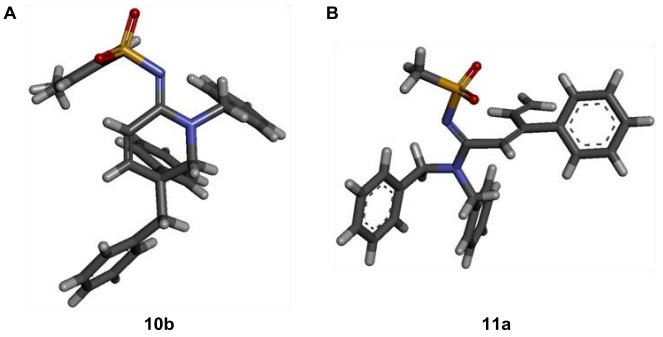


Fig. 1 Single crystal XRD structures of cyclic amidine **10b** (**A**) and acyclic amidine **11a** (**B**) presented as stick model.

Calculations on the enynamine **II** with R^1 = R^2 = Bn, and different combinations of H and Ph for R^3, R^4 corresponding to substrates **9-12** were performed using DFT (B3LYP/6-31G). In these cases, obtaining the transition state structures using the MP2 method, which is significantly more computationally demanding than DFT, is impractical. The transition state structures and consequently barrier heights using DFT corresponding to products **IIa** and **IIb** were obtained (Table S2). The transition state for **IIc** proved elusive in spite of using several techniques and initial structures to search for it. Since the MP2 barriers are more reliable, we applied a correction to the DFT barriers to estimate them better using the results of the simplified enynamine **III** where both MP2 and DFT barriers were calculated. Assuming that there are similar differences in MP2 and DFT calculated barrier heights in the present case as in **III**, we applied the calculated difference in **III** as a correction to the present case (Table S2). The corrected barrier heights uniformly predict the trends in the observed product distribution, thus supporting the proposed mechanism. Inspection of the intermediate structures suggests that a phenyl group at the C_2-center (*i.e.* for substrate **10**) increases the contributions of **IIg** and **IIh** through further delocalization of the negative charge. Enhancement of negative charge at C_2- and C_4-centers further favors the attacks on the R^1 group from these sites thereby, stabilizing corresponding transition states. In case of **11**, the phenyl group at C_3-center does not contribute significantly to the stabilization of the negative charge on the intermediate **IIf**. Therefore, **IIf** facilitates a C_1-N bond cleavage leading to the formation of [1,5]-migration product. For **12**, the substitution of phenyl groups at C_2-center again opens the scope of R^1 group migration.

Having established the effect of substituents at C_2- and C_3-centers, we next evaluated the effects of different *p*-substituted arylmethylene groups at R^1 and R^2 positions in controlling the product distribution. For enynamines **13-16**,

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB00499K

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

designed with $R^1 = R^2$ = 4-*CN*Bn, and varying R^3 and R^4 groups among H and Ph, the distributions of products were comparable to that observed with **9-12** (Entries 5-8). However, for substrates **17-20** with of $R^1 = R^2$ = 4-*MeO*Bn, an interesting bias of product distribution towards cyclic systems was observed (Entries 9-12). For example, the substrate **17** ($R^3 = R^4$ = H) upon reaction with TsN_3 gave only cyclic products **17b** (63%) and **17c** (12%). Therefore, the electron rich aromatic moiety of 4-*MeO*Bn contributes significantly in shifting the course of rearrangement towards cyclic products due to the higher migratory aptitude of the 4-*OMe*Bn group. Subsequently, the migratory aptitudes of Bn and 4-*CN*Bn groups were compared by considering enynamines **21-24**. Compound **21** ($R^3 = R^4$ = H) when reacted with TsN_3, compounds **21a-21c** were formed in 14%, 39% and 23% yields, respectively (Entry 13). Structural analysis of **21b** and **21c** clearly indicated the migration of the benzyl group to either C_2- or C_4-position (see ESI). For the substrates **21-24**, the trends in product distribution are similar to the corresponding substrates **9-12** as might have been expected (Entries 14, 16). Substrate **23** (R^3 = H and R^4 = Ph) however, gave only **23a** (86%) as expected (Entry 15). As anticipated, the substitutions on the sulfonyl group did not have any contribution in changing the product distribution for substrates **10** and **11** (Entries 17, 18).

To get an experimental evidence of the zwitterionic cyclic intermediate, a 2-vinylpiperidine substituted enynamine **27** was designed. Reaction of **27** with TsN_3 gave bicycloamidine **28** as single product (Scheme 3A) and this structure was unambiguously confirmed by X-ray crystallographic data analysis (Fig. 3A). Therefore, the ketenimine intermediate **27a** forms the cyclic intermediate **27b** which subsequently undergoes aza-Claisen rearrangement[14] by an attack from C_4- to $C_{4'}$-position followed by migration of the double bond from $C_{4'}$=$C_{3'}$ to the $C_{3'}$=$C_{2'}$, and cleavage of the $C_{2'}$–N bond (Scheme S9). Compound **11a**, a representative conjugated acyclic diene,

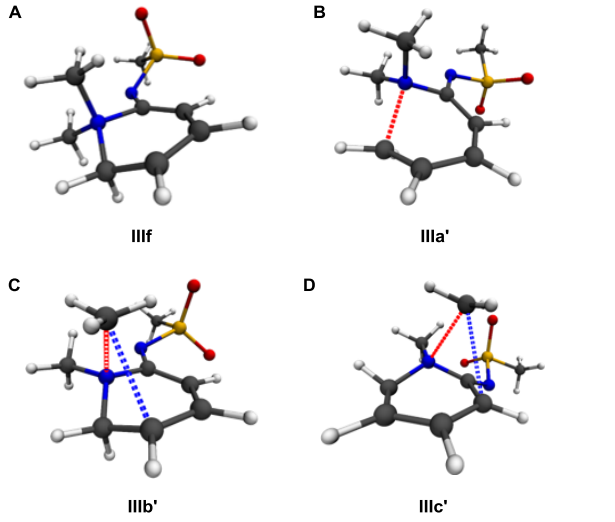
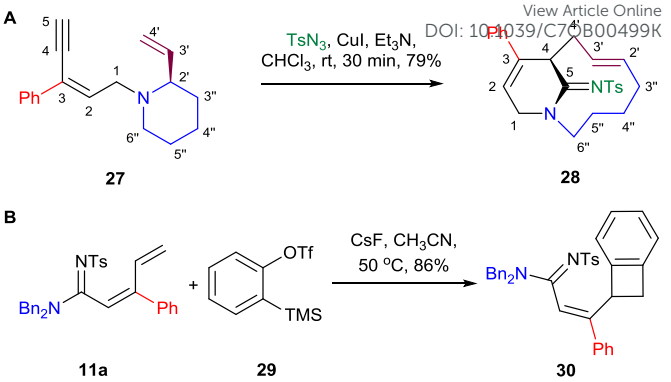


Fig. 2 Structures of the intermediate **IIIf** (**A**), and transition states **IIIa'**, **IIIb'** and **IIIc'** (**B-D**) for the formation of **IIIa**, **IIIb** and **IIIc** calculated at the MP2/6-31G level.



Scheme 3. Synthesis of bridged bicycloamidine **28** (**A**). [2+2] Cycloaddition of **11a** with *in situ* generated benzyne (**B**).

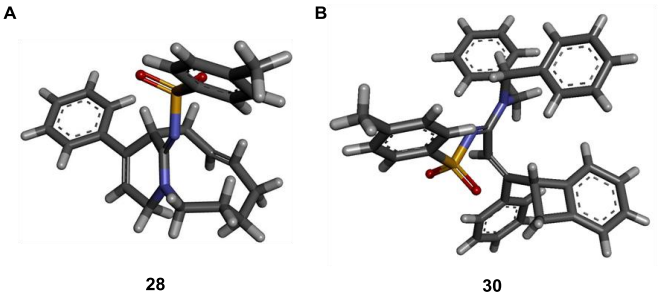


Fig. 3 Single crystal XRD structures of cyclic amidine **28** (**A**) and acyclic amidine **30** (**B**) presented as stick model.

when reacted with highly reactive benzyne, generated from **29**, compound **30** was formed as an exclusive [2+2] cycloaddition[15] product (Scheme 3B). Such observation is unique because a thermal [4+2] cycloaddition[16] is more common under the applied conditions. The structure of **30** was confirmed by X-ray crystallographic data analysis (Fig. 3B).

Conclusions

In conclusion, we have demonstrated the reaction of substituted enynamines with sulfonylazides under Cu(I) catalytic conditions providing acyclic and cyclic amidines. Structures of these products were confirmed by NMR and single crystal X-ray diffraction studies. The central carbon of *in situ* formed ketenimine was attacked by tethered amino group in the *6-exo-dig* cyclization mode followed by breaking of C-N bond in the E1cB fashion gives acyclic amidines. On the other hand, the delocalization of negative charge on the cyclic zwitterionic intermediate facilitated the transfer of a nitrogen substituent to C_3- and C_5-centers leading to the formation of cyclic amidines. The mechanism and the product distribution of these reactions were evaluated by computational studies. Two interesting applications of the strategy were illustrated through the formation of a bridged bicycloamidine and a [2+2] cycloaddition reaction.

Experimental

Organic & Biomolecular Chemistry Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

View Article Online
DOI: 10.1039/C7OB00499K

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

Organic & Biomolecular Chemistry Accepted Manuscript

General Information

All the chemicals were purchased from commercial sources and used as received unless stated otherwise. All reactions were carried out under the nitrogen atmosphere. Solvents: dichloromethane (DCM), ethyl acetate (EtOAc), methanol (MeOH) and petroleum ether, were distilled prior to thin layer and column chromatography. Column chromatographic purification was performed on silica gel (100–200 mesh). TLC was carried out with silica gel 60-F-254 plates.

The ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz Jeol 400 MHz (or 100 MHz for ^{13}C) spectrometers using either residual solvent signal as an internal reference or from internal tetramethylsilane on the δ scale ($CDCl_3$: δ_H 7.24 ppm, δ_C 77.0 ppm). The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. The following abbreviations are used: m (multiplet), s (singlet), br s (broad singlet), d (doublet), t (triplet) dd (doublet of doublet), dt (doublet of triplet), q (quartet), sex (sextet), and sept (septet). High-resolution mass spectra were recorded using Micro Mass ESTOF MS spectrometer. (FT-IR) spectra were recorded using Bruker: α ALPHA spectrophotometer (neat) and reported in cm^{-1}. Crystal structures were recorded on a Bruker single crystal X-Ray diffractometer.

General procedure for the copper catalyzed reaction of 1 with tosyl azide

The reaction conditions and results are shown in Tables 1. A typical procedure is given for the reaction of **1** with tosyl azide (Table 1, entry 1). To the solution of enynamine **1** (100 mg, 0.6 mmol) in chloroform (3.0 mL) was added tosyl azide (156 mg, 0.8 mmol), Et_3N (108 mg, 1.0 mmol) followed by CuI (12 mg, 10 mol%) and stirred for 30 minutes at room temperature. The reaction was quenched by saturated NH_4Cl and compound was extracted in chloroform (15 mL × 2). Solvent was evaporated and obtained crude product was purified by column chromatography (*Eluent*: 30% EtOAc in hexane) to afford the desired acyclic amidine product **1a** (142 mg, 67% yield) as a colorless semi-solid.

1a: IR (neat): ν_{max}/cm^{-1} 3743, 3678, 3648, 3619, 2967, 2921, 2861, 2319, 1740, 1693, 1643, 1595, 1519, 1476, 1444, 1346, 1273, 1190, 1141, 1114, 1087; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.30 (t, *J* = 11.4 Hz, 1H), 6.16 (d, *J* = 11.5 Hz, 1H), 5.96 (dt, *J* = 16.7 Hz, 10.7 Hz, 1H), 5.32 (d, *J* = 16.9 Hz, 1H), 5.21 (d, *J* = 10.0 Hz, 1H), 3.81 (t, *J* = 4.5 Hz, 2H), 3.68 (t, *J* = 5.0 Hz, 2H), 3.59 (t, *J* = 5.0 Hz, 2H), 3.46 (t, *J* = 5.0 Hz, 2H), 2.33(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 142.1, 140.2, 135.4, 131.3, 129.1, 126.9, 123.6, 120.3, 66.7, 66.3, 47.9, 44.7, 21.5; HRMS (ESI): Calc. for $C_{16}H_{21}N_2O_3S$ $[M+H]^+$: 321.1273; Found: 321.1281.

2a: Isolated yield: 76%, 132 mg. Colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 2967, 2920, 2860, 1721, 1597, 1521, 1443, 1344, 1344, 1275, 1225, 1150, 1113, 1088, 1029; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.34 (dd, *J* = 6.6, 3.3 Hz, 3H), 7.32 – 7.22 (m, 7H), 6.71 (dd, *J* = 12.4, 0.8 Hz, 1H), 6.48 (d, *J* = 12.5 Hz, 1H), 5.52 (s, 1H), 5.44 (s, 1H), 3.46 (dd, *J* = 11.3, 6.4 Hz, 4H), 3.34 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 143.8, 142.2, 140.6, 138.2, 136.4, 129.2, 128.5, 128.4, 126.7, 126.7, 120.7, 120.4, 66.3, 65.7, 47.6, 44.1, 29.8, 21.6; HRMS (ESI): Calc. for $C_{22}H_{25}N_2O_3S$ $[M+H]^+$: 397.1586; Found: 397.1584.

3a: Isolated yield: 70%, 122 mg. Colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 2967, 2920, 2860, 1721, 1597, 1521, 1443, 1344, 1344, 1275, 1225, 1150, 1113, 1088, 1029; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.35 (m, 5H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.25 (s, 1H), 6.20 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.30 (dt, *J* = 10.8, 1.2 Hz, 1H), 5.20 (d, *J* = 17.3 Hz, 1H), 3.96 – 3.89 (m, 2H), 3.80 – 3.75 (m, 2H), 3.72 – 3.67 (m, 2H), 3.62 – 3.56 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 145.2, 142.1, 140.4, 137.7, 132.1, 129.1, 128.7, 128.6, 128.5, 126.9, 122.8, 119.7, 66.7, 66.3, 47.8, 44.8, 29.8, 21.5; HRMS (ESI): Calc. for $C_{22}H_{25}N_2O_3S$ $[M+H]^+$: 397.1586; Found: 397.1584.

4a: Isolated yield: 65%, 101 mg. Colorless semi-solid. IR (neat): ν_{max}/cm^{-1} 2967, 2920, 2860, 1721, 1597, 1521, 1443, 1344, 1344, 1275, 1225, 1150, 1113, 1088, 1029; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.34 (m, 3H), 7.26 (dd, *J* = 6.7, 3.3 Hz, 2H), 7.23 – 7.19 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.79 (s, 1H), 5.86 (d, *J* = 0.6 Hz, 1H), 5.34 (s, 1H), 3.58 (s, 4H), 3.40 (s, 2H), 3.25 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.49, 148.81, 143.98, 142.01, 140.37, 139.06, 137.34, 129.04, 128.76, 128.65, 128.54, 128.18, 128.06, 127.96, 127.41, 126.88, 126.56, 119.30, 119.03, 66.11, 65.68, 48.12, 44.53, 21.49; HRMS (ESI): Calc. for $C_{28}H_{29}N_2O_3S$ $[M+H]^+$: 473.1899; Found: 473.1894.

General procedure for the copper catalyzed reaction of 9 with tosyl azide

The reaction conditions and results are shown in Tables 2. To the solution of enynamine **9** (100 mg, 0.3 mmol) in chloroform (3.0 mL) was added tosyl azide (90 mg, 0.4 mmol), Et_3N (50 mg, 0.5 mmol) followed by CuI (6.0 mg, 10 mol%) and stirred for 30 minutes at room temperature. The reaction was quenched by sat. NH_4Cl and compound was extracted in chloroform (15 mL × 2). Solvent was evaporated and obtained crude product was purified by column chromatography (*Eluent*: 20% EtOAc in hexane) to afford amidine products **9a** (38 mg, 23% yield), **9b** (84 mg, 51% yield) and **9c** (26 mg, 16% yield) as colorless semi-solids.

9a: Isolated yield: 23%, 38 mg. Colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 3744, 3027, 2925, 2864, 1739, 1692, 1639, 1533, 1484, 1383, 1342, 1273, 1139, 1083, 1026; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.31 (m, 6H), 7.24 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 6.5 Hz, 2H), 6.33 (m, 2H), 6.08 (m, 1H), 5.35 (dt, *J* = 16.7 Hz, 0.7 Hz, 1H), 5.22 (d, *J* = 10 Hz, 1H), 4.72 (br.s, 2H), 4.5 (s, 2H), 2.4 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 141.8, 137.1, 135.2, 130.2, 129.1, 128.7, 128.1, 128.1, 126.5, 126.2, 121.9, 53.2, 48.2, 21.5; HRMS (ESI): Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1793.

9b: Isolated yield: 51%, 84 mg. Colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 3742, 3029, 2924, 2863, 1740, 1691, 1638, 1531, 1481, 1382, 1340, 1270, 1137, 1081, 1025; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.33 (m, 3H), 7.24 – 7.20 (m, 9H), 6.84 (dd, *J* = 7.7 Hz, 2.3 Hz, 2H), 6.58 (dd, *J* = 9.8 Hz, 4.16 Hz, 1H), 4.92 (d, *J* = 14.4 Hz, 1H), 4.51 (d, *J* = 14.4 Hz, 1H), 3.37 (dd, *J* = 12.8 Hz, 5.6 Hz, 1H), 3.17 (dd, *J* = 12.7 Hz, 5.8 Hz, 1H), 2.67 (m, 2H), 2.41 (dd, *J* = 11.4, 4.6 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 144.0, 142.1, 141.2, 137.7, 135.9, 129.2, 128.9, 128.9, 128.7, 128.6,

View Article Online
DOI: 10.1039/C7OB00189K

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

128.1, 126.8, 126.4, 119.9, 52.8, 48.9, 37.3, 35.7, 21.6; HRMS (ESI): Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1790.

9c: Isolated yield: 16%, 26 mg. Colorless semi-solid. IR (neat): ν_{max}/cm^{-1} 3743, 3030, 2925, 2859, 1708, 1647, 1597, 1552, 1516, 1495, 1450, 1341, 1270, 1141, 1084, 1029; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.24 Hz, 2H), 7.28 – 7.21 (m, 10H), 7.09 (dd, *J* = 7.16 Hz, 1.6 Hz, 2H), 5.74 (m, 2H), 4.91 (d, *J* = 14.54 Hz, 1H), 4.74 (m, 1H), 4.26 (d, *J* = 14.6 Hz, 1H), 3.50 (m, 1H), 3.35 (dd, *J* = 13 Hz, 7.7 Hz, 1H), 3.06 (d, *J* = 17.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 141.7, 141.6, 137.0, 135.2, 130.1, 129.1, 128.7, 128.0, 128.0, 127.8, 126.6, 126.4, 126.1, 121.7, 53.1, 48.1, 40.4, 40.2, 21.4; HRMS (ESI): Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1792.

10b: Isolated yield: 50%, 75 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3008, 2931, 2838, 1621, 1577, 1534, 1514, 1467, 1441, 1381, 1275, 1246, 1174, 1140, 1113, 1084, 1032; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 10.2 Hz, 1H), 7.28 – 7.08 (m, 11H), 7.04 (d, *J* = 6.9 Hz, 2H), 6.98 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.79 (d, *J* = 10.2 Hz, 1H), 6.65 (d, *J* = 6.8 Hz, 2H), 4.81 (d, *J* = 14.6 Hz, 1H), 4.54 (d, *J* = 14.6 Hz, 1H), 3.58 (s, 2H), 3.04 (d, *J* = 13.5 Hz, 1H), 2.92 (d, *J* = 13.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 146.6, 142.0, 141.2, 140.8, 135.3, 135.2, 130.4, 129.2, 128.7, 128.4, 128.1, 127.8, 127.4, 127.0, 126.5, 126.4, 120.1, 56.2, 52.9, 44.7, 44.0, 21.6; HRMS (ESI): Calc. for $C_{32}H_{31}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2115.

10c: Isolated yield: 40%, 60 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3018, 2935, 2831, 1624, 1575, 1535, 1511, 1471, 1444, 1382, 1271, 1244, 1184, 1148, 1121, 1094, 1038; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.30 (m, 3H), 7.29 – 7.17 (m, 11H), 7.13 (m, 4H), 6.05 (dd, *J* = 5.6, 2.7 Hz, 1H), 4.94 (d, *J* = 14.5 Hz, 2H), 4.33 (d, *J* = 14.6 Hz, 1H), 3.77 (dd, *J* = 17.1, 1.7 Hz, 1H), 3.56 (dd, *J* = 13.1, 7.2 Hz, 1H), 3.29 (dd, *J* = 13.1, 3.5 Hz, 1H), 3.20 (dt, *J* = 17.1, 2.9 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 141.8, 141.6, 136.9, 135.0, 133.4, 130.2, 129.1, 128.7, 128.7, 128.2, 128.1, 128.0, 127.8, 126.7, 126.2, 124.9, 122.3, 53.3, 49.9, 40.8, 40.4, 21.4; HRMS (ESI): Calc. for $C_{32}H_{31}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2115.

11a: Isolated yield: 84%, 126 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3740, 3025, 2922, 2862, 1733, 1690, 1635, 1530, 1480, 1381, 1341, 1271, 1135, 1081, 1022; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.28 (m, 13H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.16 (dd, *J* = 8.1 Hz, 1.7 Hz, 2H), 6.33 (s, 1H), 6.22 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 5.21 (dt, *J* = 10.8 Hz, 1.2 Hz, 1H), 5.13 (dd, *J* = 17.2 Hz, 0.84 Hz, 1H), 4.59 (br.s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 144.8, 142.0, 140.7, 137.9, 135.8, 135.2, 132.1, 129.2, 129.1, 128.9, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 127.4, 126.9, 122.5, 120.5, 51.9, 50.0, 21.5; HRMS (ESI): Calc. for $C_{32}H_{31}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2106.

11b: Isolated yield: 5%, 8 mg. Colorless semi-solid. IR (neat): ν_{max}/cm^{-1} 3740, 3025, 2921, 2861, 1743, 1693, 1635, 1535, 1485, 1384, 1342, 1273, 1135, 1085, 1021; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.60 (m, 3H), 7.43 (m, 3H), 7.32 (m, 3H), 7.26 (m, 5H), 7.11 (m, 3H), 6.53 (dd, *J* = 7.2 Hz, 3.7 Hz, 2H), 5.09 (d, *J* = 14.3 Hz, 1H), 4.39 (d, *J* = 14.3 Hz, 1H), 3.47 (dd, *J* = 13.2 Hz, 5.0 Hz, 1H), 3.23 (d, *J* = 13.2 Hz, 1H), 3.02 (m, 1H), 2.59 (dd, *J* = 14.0 Hz, 3.16 Hz, 1H), 2.39 (s, 3H), 2.31 (dd, *J* = 14.0 Hz, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 153.7, 142.0, 141.5, 138.3, 136.1, 135.9, 130.5, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.2, 127.0, 126.7, 126.4, 114.7, 52.6, 47.2, 38.0, 36.1, 21.5; HRMS (ESI): Calc. for $C_{32}H_{31}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2110.

12a: Isolated yield: 48%, 68 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3744, 3035, 2933, 2866, 1723, 1688, 1645, 1538, 1481, 1382, 1342, 1275, 1138, 1088, 1021; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.34 (m, 6H), 7.31 (m, 6H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.01 (m, 10H), 6.90 (s, 1H), 5.69 (d, *J* = 0.6 Hz, 1H), 5.37 (d, *J* = 0.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.9, 148.0, 142.7, 141.9, 140.6, 138.8, 137.1, 135.5, 135.3, 129.1, 129.1, 129.0, 128.9, 128.6, 128.4, 128.3, 128.1, 127.8, 127.7, 127.2, 127.1, 126.8, 126.7, 119.6, 119.3, 52.2, 49.6, 21.5; HRMS (ESI): Calc. for $C_{38}H_{35}N_2O_2S$ $[M+H]^+$: 583.2419; Found: 583.2430.

12c: Isolated yield: 30%, 43 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3738, 3032, 2925, 2867, 1722, 1687, 1638, 1531, 1483, 1382, 1344, 1277, 1133, 1077, 1032; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 4H), 7.63 (s, 2H), 7.42 – 7.31 (m, 7H), 7.28 – 7.13 (m, 23H), 7.13 – 7.02 (m, 8H), 6.76 (d, *J* = 7.5 Hz, 4H), 6.61 (d, *J* = 7.4 Hz, 4H), 4.92 (d, *J* = 14.7 Hz, 2H), 4.06 (d, *J* = 14.7 Hz, 2H), 3.91 (d, *J* = 13.0 Hz, 2H), 3.46 (d, *J* = 14.3 Hz, 2H), 3.39 (d, *J* = 13.0 Hz, 2H), 3.26 (d, *J* = 14.3 Hz, 2H), 2.41 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.52, 156.04, 141.74, 141.46, 141.31, 137.96, 135.91, 134.88, 130.55, 129.29, 129.01, 128.73, 128.49, 128.46, 128.37, 128.02, 128.01, 127.45, 127.33, 127.14, 126.90, 126.37, 121.50, 57.74, 52.28, 47.61, 42.00, 21.46; HRMS (ESI): Calc. for $C_{38}H_{35}N_2O_2S$ $[M+H]^+$: 583.2419; Found: 583.2420.

13a: Isolated yield: 13%, 20 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3022, 2918, 2218, 1713, 1625, 1545, 1488, 1441, 1412, 1338, 1276, 1225, 1178, 1141, 1083, 1021; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 – 7.67 (m, 4H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 4H), 6.43 (t, *J* = 11.4 Hz, 1H), 6.24 (d, *J* = 11.6 Hz, 1H), 6.05 (dt, *J* = 16.8, 10.6 Hz, 1H), 5.42 (d, *J* = 16.7 Hz, 1H), 5.31 (d, *J* = 10.1 Hz, 1H), 4.77 – 4.66 (m, 2H), 4.61 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 142.6, 140.8, 140.1, 139.7, 136.1, 133.0, 132.6, 130.9, 129.1, 129.0, 127.8, 126.7, 124.4, 119.9, 52.2, 50.3, 29.7, 21.5; HRMS (ESI): Calc. for $C_{28}H_{25}N_4O_2S$ $[M+H]^+$: 481.1698; Found: 481.1702.

13b: Isolated yield: 37%, 57 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3013, 2927, 2238, 1711, 1609, 1552, 1491, 1452, 1422, 1345, 1273, 1218, 1171, 1141, 1086, 1021; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.59 (dd, *J* = 8.4, 3.4 Hz, 4H), 7.29 (dd, *J* = 13.3, 8.4 Hz, 6H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.56 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.77 (d, *J* = 15.0 Hz, 1H), 4.64 (d, *J* = 15.0 Hz, 1H), 3.44 (dd, *J* = 12.9, 5.5 Hz, 1H), 3.18 (dd, *J* = 12.8, 6.6 Hz, 1H), 2.86 – 2.75 (m, 2H), 2.63 (td, *J* = 10.6, 3.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.70, 143.30, 142.87, 141.22, 140.65, 138.71, 132.67, 132.63, 129.67, 129.34, 128.90, 128.67, 126.34, 120.38, 118.74, 111.20, 55.88, 52.91, 50.07, 37.67, 35.18, 21.59; HRMS (ESI): Calc. for $C_{28}H_{25}N_4O_2S$ $[M+H]^+$: 481.1698; Found: 481.1699.

13c: Isolated yield: 23%, 35 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3018, 2925, 2226, 1702, 1601, 1554, 1491, 1447, 1414, 1344, 1269, 1209, 1174, 1149, 1088, 1011; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J*

Organic & Biomolecular Chemistry Accepted Manuscript

 This journal is © The Royal Society of Chemistry 20xx

View Article Online
DOI: 10.1039/C7OB00499K

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

= 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.83 (dd, *J* = 10.0, 4.1 Hz, 1H), 5.77 (dd, *J* = 8.6, 4.0 Hz, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 4.77 (s, 1H), 4.18 (d, *J* = 15.1 Hz, 1H), 3.64 (d, *J* = 15.7 Hz, 1H), 3.38 (m, 3H), 2.98 (s, 3H), 2.90 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 142.7, 142.4, 140.8, 140.5, 132.5, 131.9, 130.7, 129.2, 128.2, 126.1, 126.0, 121.9, 118.8, 118.3, 111.7, 110.8, 53.1, 49.0, 40.5, 39.9, 21.5; HRMS (ESI): Calc. for $C_{28}H_{25}N_4O_2S$ $[M+H]^+$: 481.1698; Found: 481.1697.

14b: Isolated yield: 51%, 73 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3019, 2926, 2228, 1703, 1605, 1555, 1498, 1446, 1415, 1343, 1270, 1215, 1173, 1140, 1083, 1019; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 10.2 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.15 (m, 6H), 6.92 (t, *J* = 7.4 Hz, 4H), 6.76 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 10.3 Hz, 1H), 5.02 (d, *J* = 15.1 Hz, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.64 (d, *J* = 12.9 Hz, 1H), 3.56 (d, *J* = 12.9 Hz, 1H), 3.13 (d, *J* = 13.4 Hz, 1H), 2.96 (d, *J* = 13.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 145.3, 142.4, 140.5, 140.5, 139.8, 132.3, 131.9, 130.9, 129.2, 128.9, 128.5, 127.9, 126.4, 126.3, 120.7, 118.4, 111.5, 111.2, 57.5, 52.7, 44.53, 44.1, 21.5; HRMS (ESI): Calc. for $C_{34}H_{29}N_4O_2S$ $[M+H]^+$: 557.2011; Found: 557.2012.

14c: Isolated yield: 32%, 46 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3024, 2922, 2222, 1706, 1603, 1551, 1495, 1444, 1411, 1347, 1277, 1214, 1173, 1142, 1085, 1012; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.31 (m, 3H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.17 – 7.10 (m, 4H), 6.02 (dd, *J* = 5.5, 2.6 Hz, 1H), 4.96 (d, *J* = 15.2 Hz, 2H), 4.24 (d, *J* = 15.1 Hz, 1H), 3.89 (dd, *J* = 17.1, 1.7 Hz, 1H), 3.55 (dt, *J* = 17.1, 2.8 Hz, 1H), 3.44 (qd, *J* = 13.0, 5.7 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.31, 142.84, 142.55, 140.76, 140.42, 136.10, 133.27, 132.62, 132.00, 130.86, 129.30, 129.09, 128.87, 128.33, 126.11, 124.81, 121.66, 118.85, 118.41, 111.92, 111.03, 53.29, 50.71, 40.74, 40.40, 21.58; HRMS (ESI): Calc. for $C_{34}H_{29}N_4O_2S$ $[M+H]^+$: 557.2011; Found: 557.2012.

15a: Isolated yield: 77%, 110 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3022, 2924, 2226, 1703, 1605, 1555, 1498, 1444, 1414, 1343, 1275, 1210, 1170, 1145, 1085, 1018; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.1 Hz, 4H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.36 (m, 4H), 7.35 (s, 1H), 7.31 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.27 (s, 1H), 6.20 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 5.23 (d, *J* = 17.3 Hz, 1H), 4.68 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.86, 145.69, 142.59, 140.78, 140.31, 139.84, 137.36, 133.01, 132.56, 131.82, 129.16, 128.85, 128.51, 128.45, 127.83, 126.75, 123.41, 119.20, 118.31, 118.07, 112.54, 112.08, 52.41, 50.57, 21.50; HRMS (ESI): Calc. for $C_{34}H_{29}N_4O_2S$ $[M+H]^+$: 557.2011; Found: 557.2018.

16a: Isolated yield: 73%, 100 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3025, 2921, 2227, 1708, 1601, 1554, 1496, 1432, 1411, 1348, 1275, 1213, 1173, 1141, 1088, 1011; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.34 (m, 6H), 7.23 – 7.13 (m, 10H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.86 (s, 1H), 5.79 (d, *J* = 0.5 Hz, 1H), 5.40 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.2, 149.1, 143.1, 142.6, 140.5, 140.4, 139.8, 138.3, 136.6, 132.9, 132.2, 129.2, 129.2, 128.8, 128.6, 127.5, 127.1, 126.7, 126.4, 119.1, 118.5, 112.4, 111.8, 52.7, 50.2, 21.5; HRMS (ESI): Calc. for $C_{40}H_{34}N_4O_2S$ $[M+H]^+$: 633.2324; Found: 633.2317.

16b: Isolated yield: 18%, 25 mg. Colorless semi-solid. IR (neat): ν/cm^{-1} 3018, 2920, 2216, 1711, 1612, 1542, 1491, 1438, 1410, 1339, 1268, 1251, 1179, 1133, 1085, 1013; δ 7.65 (d, *J* = 5.8 Hz, 6H), 7.62 (s, 3H), 7.38 – 7.29 (m, 17H), 7.23 (d, *J* = 8.2 Hz, 8H), 7.22 – 7.16 (m, 19H), 7.14 (d, *J* = 7.9 Hz, 6H), 6.69 (dd, *J* = 8.1, 5.8 Hz, 12H), 5.13 (d, *J* = 15.1 Hz, 3H), 3.95 (d, *J* = 12.7 Hz, 3H), 3.81 (d, *J* = 15.1 Hz, 3H), 3.51 (d, *J* = 14.3 Hz, 3H), 3.37 (d, *J* = 12.8 Hz, 3H), 3.30 (d, *J* = 14.4 Hz, 3H), 2.40 (s, 10H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.30, 141.37, 140.92, 140.71, 140.43, 137.43, 132.12, 131.72, 131.22, 129.88, 129.14, 129.03, 128.86, 128.26, 128.13, 127.99, 127.01, 126.30, 121.59, 118.53, 118.43, 111.12, 111.00, 58.58, 52.07, 47.83, 42.07, 21.49; HRMS (ESI): Calc. for $C_{40}H_{34}N_4O_2S$ $[M+H]^+$: 633.2324; Found: 633.2321.

Crystallography

Crystal structure of compound 11a (CCDC 1525177): $C_{26}H_{26}N_2O_2S$; Compound **11a** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *C2/c*; *a* = 27.148(6) *b* = 6.2305(14) *c* = 27.401(6) Å, α = 90° β = 92.154° γ = 90°; *V* = 4631.5(18) Å^3; *T* = 296 (2) K; *Z* = 8; ρ_{calc} = 1.235 Mgm^{-3}; ϑ_{max}= 26.37°; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. *R* = 0.0514 (for 2576 reflection *I>2σ(I)*), *wR* = 0.1764 which was refined against |*F2*| and S = 0.941 for 281 parameters and 4739 unique reflections. The structure was obtained by direct methods using SHELXS-97. All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the fil cycle of refinement as riding over atoms to which they are bonded. μ = 0.164 mm^{-1}.

Crystal structure of compound 10b (CCDC 1525176): $C_{32}H_{30}N_2O_2S$; Compound **10b** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *P21/c*; *a* = 8.0697(3) *b* = 32.4621(12) *c* = 9.8721(4) Å, α = 90° β = 90.5490° γ = 90°; *V* = 2585.97(17) Å^3; *T* = 296 (2) K; *Z* = 4; ρ_{calc} = 1.301 Mgm^{-3}; ϑ_{max} = 68.384°; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. *R* = 0.0434 (for 4143 reflection *I>2σ(I)*), *wR* = 0.1365 which was refined against |*F2*| and S = 1.101 for 335 parameters and 4726 unique reflections. The structure was obtained by direct methods using SHELXS-97. All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over atoms to which they are bonded. μ = 1.364 mm^{-1}.

Crystal structure of compound 28 (CCDC 1525520): $C_{25}H_{28}N_2O_2S$; Compound **28** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group P^{-1}; *a* = 9.0423(4) *b* = 10.9846(5) *c* = 11.4374(5) Å, α =

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/C7OB01249K

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

91.995° β = 100.164° γ = 103.818°; V = 2128.3(8) Å^3; T = 0 (2) K; Z = 2; ρ_{calc} = 1.291 Mgm^{-3}; ϑ_{max} = 54.76°; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0361 (for 4159 reflection $I>2\sigma(I)$), wR = 0.0820 which was refined against |$F2$| and S = 0.935 for 258 parameters and 4839 unique reflections. The structure was obtained by direct methods using SHELXS-97. All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over atoms to which they are bonded. μ = 0.174 mm^{-1}.

Crystal structure of compound 30 (CCDC 1525179): $C_{38}H_{34}N_2O_2S$; Compound **30** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *P21/c*; a = 12.375(4) b = 17.958(7) c = 14.179(6) Å, α = 90° β = 91.594° γ = 90°; V = 3150(2) Å^3; T = 296 (2) K; Z = 4; ρ_{calc} = 1.229 Mgm^{-3}; ϑ_{max}= 28.282°; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0805 (for 2133 reflection $I>2\sigma(I)$), wR = 0.2471 which was refined against |$F2$| and S = 0.912 for 389 parameters and 5734 unique reflections. The structure was obtained by direct methods using SHELXS-97. All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over atoms to which they are bonded. μ = 0.139 mm^{-1}.

Crystal structure of compound 22b (CCDC 1525178): $C_{33}H_{29}N_3O_2S$; Compound **22b** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group P^{-1}; a = 8.7353(11) b = 10.2521(13) c = 15.765(2) Å, α = 101.925° β = 98.258° γ = 93.270°; V = 1361.6(3) Å^3; T = 296 (2) K; Z = 2; ρ_{calc} = 1.334 Mgm^{-3}; ϑ_{max} = 77.283°; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0948 (for 4453 reflection $I>2\sigma(I)$), wR = 0.2636 which was refined against |$F2$| and S = 1.782 for 353 parameters and 5550 unique reflections. The structure was obtained by direct methods using SHELXS-97. All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over atoms to which they are bonded. μ = 1.334 mm^{-1}.

Notes and references

1 (a) T. T. Tidwell, *Pure Appl. Chem.*, 1997, **69**, 211; (b) J. E. Leffler, *The Reactive Intermediates of Organic Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1956, p 67.

2 (a) G. R. Krow, *Angew. Chem., Int. Ed.*, 1971, **10**, 435; (b) H. Hopf, The Chemistry of Functional Groups. In *The chemistry of ketenes, allenes, and related compounds*; S. Patai, Ed.; John Wiley & Sons: Chichester, 1980; Vol. II, pp 779-901; (c) E. J. Yoo and S. Chang, *Curr. Org. Chem.*, 2009, **13**, 1766; (d) P. Lu and Y. Wang, *Synlett,* 2010, 165; (e) M. Alajarin, A. Vidal and F. Tovar, *Targets Heterocycl. Syst.*, 2000, **4**, 293; (f) H. Perst, *Sci. Synth.*, 2006, **23**, 781; (g) P. Lu and Y. Wang, *Chem. Soc. Rev.*, 2012, **41**, 5687; (h) M. Alajarin, M. Marin-Luna and A. Vidal, *Eur. J. Org. Chem.*, 2012, **2012**, 5637; (i) S. H. Kim, S. H. Park, J. H. Choi, and S. Chang, *Chem. Asian J.*, 2011, **6**, 2618.

3 (a) Y. Zhang, K. A. DeKorver, A. G. Lohse, Y.-S. Zhang, J. Huang and R. P. Hsung, *Org. Lett.*, 2009, **11**, 899; (b) K. A. De Korver, R. P. Hsung, A. G. Lohse and Y. Zhang, *Org. Lett.*, 2010, **12**, 1840; (c) K. A. DeKorver, W. L. Johnson, Y. Zhang, R. P. Hsung, H. Dai, J. Deng, A. G. Lohse and Y.-S. Zhang, *J. Org. Chem.*, 2011, **76**, 5092; (d) I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 2038; (e) J. Y. Kim, S. H. Kim and S. Chang, *Tetrahedron Lett.,* 2008, **49**, 1745; (f) J. Kim, S. Y. Lee, J. Lee, Y. Do and S. Chang, *J. Org. Chem.*, 2008, **73**, 9454; (g) E. J. Yoo, I. Bae, S. H. Cho, H. Han and S. Chang, *Org. Lett.*, 2006, **8**, 1347; (h) S. H. Cho, E. J. Yoo, I. Bae and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 16046.

4 H.-D. Xu, M.-Q. Cai, W.-J. He, W.-H. Hu and M.-H. Shen, *RSC Adv.,* 2014, **4**, 7623.

5 (a) A. Van Camp, D. Goossens, M. Moya-Portuguez, J. Marchand-Brynaert and L. Ghosez, *Tetrahedron Lett.*, 1980, **21**, 3081; (b) G. Wulff, U. Schroeder and W. Schmidt, *Angew. Chem.*, 1979, **91**, 337; (c) M. Alajarin, P. Molina and A. Vidal, *Tetrahedron Lett.*, 1996, **37**, 8945; (d) M. Alajarin, P. Molina, A. Vidal and F. Tovar, *Tetrahedron*, 1997, **53**, 13449.

6 (a) M. Alajarin, A. Vidal and M.-M. Ortin, *Tetrahedron Lett.*, 2003, **44**, 3027; (b) M. Alajarin, A. Vidal and M.-M. Ortin, *Org. Biomol. Chem.*, 2003, **1**, 4282; (c) M. Alajarin, A. Vidal, M.-M. Ortin and D. Bautista, *New J. Chem.*, 2004, **28**, 570; (d) M. Alajarin, A. Vidal, M.-M. Ortin and D. Bautista, *Synlett*, 2004, 991; (e) M. Schmittel, J.-P. Steffen, M. A. W. Angel, B. Engels, C. Lennartz and M. Hanrath, *Angew. Chem., Int. Ed.*, 1998, **37**, 1562.

7 (a) L. Brandsma, A. L. Spek, B. A. Trofimov, O. A. Tarasova, N. A. Nedolya, A. V. Afonin and S. V. Zinshenko, *Tetrahedron Lett.*, 2001, **42**, 4687; (b) P. Molina, M. Alajarin, A. Vidal, J. Feneau-Dupont and J. P. Declercq, *J. Chem. Soc., Chem. Commun.*, 1990, 829; (c) P. Molina, M. Alajarin, A. Vidal, J. Fenau-Dupont and J. P. Declerq, *J. Org. Chem.*, 1991, **56**, 4008.

8 (a) P. Molina, M. Alajarin, C. Lopez-Leonardo and J. Alcantara, *Tetrahedron*, 1993, **49**, 5153; (b) M. A. Walters, C. S. McDonough, P. S. Brown, Jr. and A. B. Hoem, *Tetrahedron Lett.*, 1991, **32**, 179.

9 D. P. Chauhan, S. J. Varma, A. Vijeta, P. Banerjee and P. Talukdar, *Chem. Commun.*, 2014, **50**, 323.

10 (a) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1730; (b) E. J. Yoo, M. Ahlquist, I. Bae, K. B. Sharpless, V. V. Fokin and S. Chang, *J. Org. Chem.*, 2008, **73**, 5520; (c) S. J. Hwang, S. H. Cho and S. Chang, *Pure Appl. Chem.*, 2008, **80**, 873.

11 J. E. Baldwin, *J. Chem. Soc., Chem. Commun*., 1976, 734.

12 (a) R. M. Coates, J. W. Muskopf and P. A. Senter, *J. Org. Chem.*, 1985, **50**, 3541; (b) K. Ruck-Braun and C. Moller, *Chem. Eur. J.*, 1999, **5**, 1038; (c) Y. Peng, M. Yu and L. Zhang, *Org. Lett.,* 2008, **10**, 5187.

13 C. E. Check and T. M. Gilbert, *J. Org. Chem.*, 2005, **70**, 9828.

14 (a) *The Claisen Rearrangement Methods and Applications*; U. Nubbemeyer and M. Hiersemann, Eds.; Wiley-VCH: Weinheim, 2007; p 591; (b) T. P. Yoon and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 2911; (c) T. P. Yoon, V. M. Dong and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 1999, **121**, 9726; (d) H.-D. Xu, Z.-H. Jia, K. Xu, M. Han, S.-N. Jiang, J. Cao, J.-C. Wang and M.-H. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 9284.

Organic & Biomolecular Chemistry Accepted Manuscript

 This journal is © The Royal Society of Chemistry 20xx

View Article Online
DOI: 10.1039/C7OB00499K

15 (a) H. Heaney and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2693; (b) P. Crews and J. Beard, *J. Org. Chem.*, 1973, **38**, 522; (c) T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka and O. Kusama, *J. Chem. Soc. C*, 1971, 1051; (d) J. B. Feltenberger, R. Hayashi, Y. Tang, E. S. C. Babiash and R. P. Hsung, *Org. Lett.*, 2009, **11**, 3666.

16 The compound **11a** was also inert to dienophiles *e.g.* diphenylacetylene and ethyl vinyl ether even under refluxed conditions.

Published on 09 May 2017. Downloaded by Fudan University on 09/05/2017 18:04:49.

Organic & Biomolecular Chemistry Accepted Manuscript