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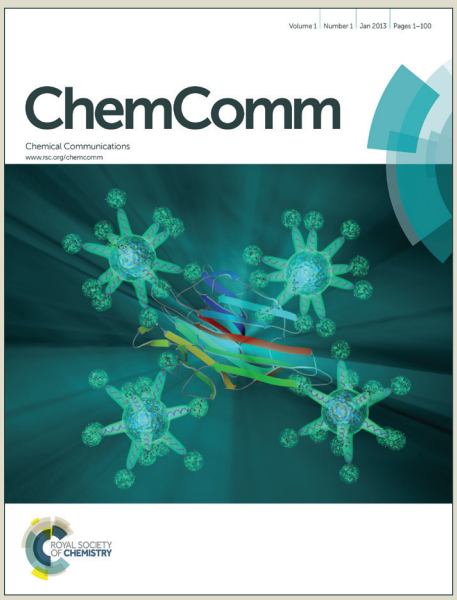

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Formal [4+2] Annulation of Enaminones and Cyanomethyl Sulfur Ylide: One-pot Access to Polysubstituted Pyridin-2(1*H*)-ones

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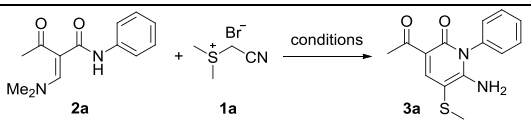
A facile and efficient one-pot synthesis of polysubstituted pyridin-2(1*H*)-ones from readily available enaminones and cyanomethyl sulfonium bromide salt in the presence of cesium carbonate is developed, and a mechanism involving sequential nucleophilic vinylic substitution (S_NV), intramolecular nucleophilic cyclization and dealkylation reactions is proposed.

Over the past decades, pyridin-2(1*H*)-ones have attracted considerable research interest since they are distributed in numerous natural products and synthetic organic compounds along with diverse useful bio-activities.[1] For instance, they constitute the skeleton of elfamycin antibiotics, the antifungal compound ilicolicin and anticancer alkaloid camptothecin.[2] The pharmaco-logical importance of pyridin-2(1*H*)-ones and their utility as versatile intermediates in the synthesis of a wide variety of nitrogen heterocycles have directed extensive research activity towards the construction of the skeleton of such kind of heterocycles.[3] To date, a variety of synthetic approaches have been well established to access pyridin-2(1*H*)-ones and their analogues, including the modification of the pre-constructed heterocyclic ring by pyridinium salt chemistry[4] and *N*-alkylation,[5] and the construction of heterocyclic skeletons from appropriately substituted open-chain precursors *via* metal-catalyzed sp^2 C-H bond amination,[6] ring closing metathesis,[7] and Diels-Alder reaction.[8] In spite of the successful pioneering work, the aforementioned reactions may suffer from either tedious synthetic procedures or utilization of metal catalyst in the synthesis. Thus, the development of efficient and convenient synthetic approaches for such aza-heterocycles is still desirable.[9]

On the other hand, the sulfur ylide mediated protocol has emerged as a powerful strategy.[10,11] Since the identification of sulfur ylides as methylene transfer agents,[12] these intermediates have been widely used in the synthesis of three-membered ring compounds, such as epoxides, aziridines and cyclopropanes.[13-15] During the course of our studies on *β*-oxo amides, we achieved facile synthesis of pyridones,[16] pyrimidinones,[17] pyridines,[18] isoxazoles,[19] cyclophosphamide[20] and pyrrolin-4-ones[21] *via* the reactions of varied enaminones derived from *β*-oxo amides. Most recently, we developed an efficient synthesis of *γ*-lactams from Corey-Chaykovsky reaction of *α*,*α*-dialkyl *β*-oxo amides and trimethylsulfoxonium iodide.[22] Inspired by these results and in continuation with our research interest in the synthesis of highly valuable heterocycles, we investigated the reaction of enaminones with cyanomethyl sulfonium bromide salt in the presence of Cs_2CO_3. As a result of this study, we achieved a facile synthesis of substituted pyridin-2(1*H*)-ones. Herein, we wish to report our experimental results and present a proposed mechanism involved in the formal [4+2] annulation reaction.

The substrates, enaminones **2**, were prepared from commercially available activated methylene amides and *N*,*N*-dimethyl formamide dimethyl acetal (DMFDMA) in the presence of K_2CO_3 according to our reported procedure.[16b] We selected 2-[(dimethylamino)methylene]-3-oxo-*N*-phenylbutanamide **2a** as a model compound to investigate its reaction behavior. Thus, the reaction of **2a** and cyanomethyl sulfonium bromide salt **1a** (1.2 equiv.)[23] in the presence of Cs_2CO_3 (1.5 equiv.) in DMSO was first attempted at room temperature. As indicated by TLC, the reaction occurred and furnished a yellow solid after work-up and purification of the resulting mixture by column chromatography. The product was characterized as 3-acetyl-6-amino-5-(methyl thio)-1-phenyl pyridin-2(1*H*)-one **3a** on the basis of its spectral and analytical data (Table 1, entry 1).

Table 1 Reaction of **2a** and Cyanomethyl Sulfonium Bromide Salt under Different Conditions.



2a **1a** **3a**

Entry	base (equiv)	solvent	Temp. (°C)	Time (h)	Yield[a] (%)
1	Cs_2CO_3(1.5)	DMSO	rt	15.0	28
2	Cs_2CO_3(3.0)	DMSO	rt	10.0	45
3	Cs_2CO_3(3.0)	DMSO	80	2.0	76
4	**Cs_2CO_3(3.0)**	**DMSO**	**100**	**1.5**	**85**
5	Cs_2CO_3(2.0)	DMSO	100	4.0	62
6	Cs_2CO_3(3.0)	Toluene	100	6.0	47
7	Cs_2CO_3(3.0)	DMF	100	1.5	78
8	Cs_2CO_3(3.0)	MeCN	reflux	6.0	44
9	NaH(3.0)	DMSO	100	8.5	79
10	NaOH(3.0)	DMSO	100	2.5	68
11	DBU(3.0)	DMSO	100	2.5	70
12	EtONa(3.0)	EtOH	reflux	12.0	65

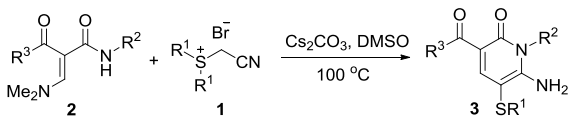
[a] Isolated yield for **3a**.

The optimization of the reaction conditions, including the reaction temperature, solvent and base, was then investigated as shown in Table 1. Increase of the amount of Cs_2CO_3 (Table 1, entry 2) and the reaction temperature (Table 1, entries 3-5) had significant influence on the yield of **3a** and the reaction time. The reaction could also proceed in other solvents, such as toluene,

DMF and acetonitrile, but the yield of **3a** was not as good as in DMSO (Table 1, entries 6-8). Other inorganic and organic bases, such as NaH, DBU, NaOH and NaOEt, were also examined, but either lower yield of **3a** was obtained or prolonged reaction time was required (Table 1, entry 9-12).

Under the conditions as for **3a** in entry 4 (Table 1), a range of reactions of enaminones **2** and cyanomethyl sulfonium bromide salts **1** were carried out, and some of the results are listed in Table 2. It was found that the enaminones **2** bearing varied aryl and alkyl groups R^2 could proceed efficiently to afford the corresponding pyridin-2(1*H*)-ones **3b-i** in good yields (Table 2, entries 2-9). The versatility of this pyridin-2(1*H*)-one synthesis was further evaluated by the reaction of **2j-m** bearing a carbamoyl, benzoyl and ethoxycarbonyl group at *α*-position with sulfonium bromide salt **1a** in the presence of Cs_2CO_3 in DMSO (Table 2, entry 10-13). The cyclization reaction proved to be suitable for sulfonium bromide salt **1b** with cyanomethyl sulfonium bromide salt **2b**, to afford the corresponding substituted pyridin-2(1*H*)-one **3n** in moderate yield (Table 2, entry 14). It should be mentioned that the structure of **3f** was further confirmed by X-ray single crystal analysis and its spectral and analytical data (Figure 1).

Table 2 Reaction of Enaminones **2** and Cyanomethyl Sulfonium Bromide Salt **1**[a].



entry	**2**	R^2	R^3	**1**	R^1	**3**	Yield[b] (%)
1	**2a**	Ph	Me	**1a**	Me	**3a**	85
2	**2b**	2- ClC_6H_4	Me	**1a**	Me	**3b**	87
3	**2c**	2-MeC_6H_4	Me	**1a**	Me	**3c**	83
4	**2d**	2-$MeOC_6H_4$	Me	**1a**	Me	**3d**	76
5	**2e**	3-MeC_6H_4	Me	**1a**	Me	**3e**	82
6	**2f**	4- $MeOC_6H_4$	Me	**1a**	Me	**3f**	80
7	**2g**	4-ClC_6H_4	Me	**1a**	Me	**3g**	88
8	**2h**	2,4-$Me_2C_6H_3$	Me	**1a**	Me	**3h**	82
9	**2i**	Bn	Me	**1a**	Me	**3i**	68
10	**2j**	Ph	PhNH	**1a**	Me	**3j**	43
11	**2k**	Ph	Ph	**1a**	Me	**3k**	46
12	**2l**	4- $MeOC_6H_4$	EtO	**1a**	Me	**3l**	54
13	**2m**	4- MeC_6H_4	EtO	**1a**	Me	**3m**	52
14	**2b**	2-ClC_6H_4	Me	**1b**	Et	**3n**	61

[a] Reagents and conditions: **2** (1.0 mmol), **1** (1.2 mmol), Cs_2CO_3 (3.0 mmol), DMSO (4.0 mL), 100 °C, 1.0-2.0 h. [b] Isolated yields.

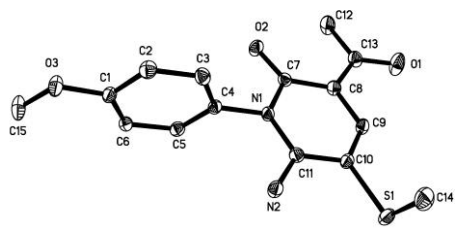
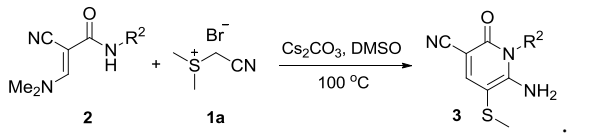


Fig. 1 ORTEP drawing of **3f**.

Table 3 Expansion of the Scope of the Pyridin-2(1*H*)-ones Synthesis[a].

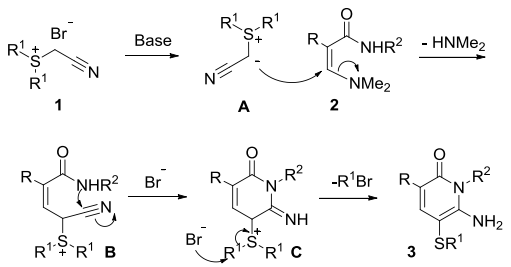


entry	**2**	R^2	**3**	Yield[b] (%)
1	**2o**	Ph	**3o**	52
2	**2p**	4-ClC_6H_4	**3p**	56
3	**2q**	4-$MeOC_6H_4$	**3q**	51

[a] Reagents and conditions: **2** (1.0 mmol), **1a** (1.2 mmol), Cs_2CO_3 (3.0 mmol), DMSO (4.0 mL), 100 °C, 1.0-2.0 h. [b] Isolated yields.

To expand the general applicability of the synthesis of pyridin-2(1*H*)-ones, we next investigated the reaction of enaminones **2** bearing cyano group at *α*-position with sulfonium bromide salt **1a** under the identical conditions. To our delight, the selected enaminones **2o-q** underwent formal [4+2] annulation reactions to furnish the corresponding pyridin-2(1*H*)-ones **3o-q** in moderate yield, respectively (Table 3, entries 1-3). All the results demonstrated the efficiency and synthetic value of the formal [4+2] annulation reaction of enaminones **2** and sulfonium bromide salts **1** as one-pot access to substituted pyridin-2(1*H*)-one of type **3**. It is worth noting that the richness of functionality, such as amino, alkylthio and carbonyl (or cyano) groups on the pyridin-2(1*H*)-one ring of **3**, may render them as building blocks for further transformation.[24]

On the basis of the above experimental results together with related literature reports, we proposed a plausible mechanism for the synthesis of pyridin-2(1*H*)-ones **3** from enaminones **2** and cyanomethyl sulfonium bromide salts **1** as depicted in Scheme 1. In the presence of Cs_2CO_3, cyanomethyl sulfonium bromide salt is converted into a stabilized sulfur ylide **A**,[10] which attacks enaminone **2** to afford the intermediate **B** *via* a nucleophilic vinylic substitution (S_NV)[25] along with the elimination of dimethylamine. Subsequent intramolecular aza-cyclization of **B** generates the iminopyridin-2(1*H*)-one intermediate **C**, followed by the dealkylation[26] in the presence of bromide ion to give rise to the final product pyridin-2(1*H*)-one **3**.



Scheme 1 Plausible Mechanism for the Reaction of Enaminones **2** with Cyanomethyl Sulfonium Bromide Salt **1**.

In summary, a facile and efficient synthesis of multi-substituted pyridin-2(1*H*)-ones is developed *via* a formal [4 + 2] annulation of enaminones with cyanomethyl sulfonium bromide salt, which involves sequential nucleophilic vinylic substitution, intramolecular nucleophilic cyclization and dealkylation reactions. The ready availability of substrates, mild reaction conditions, simplicity of execution, and synthetic potential of the products make this novel protocol very attractive. Further work on the utilization and extension of the scope of the methodology is currently under investigation in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, and spectra copies of all new compounds. CCDC 1013387. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x

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