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Synthesis of spiro[isoquinolinone-4,2′-oxiranes] and isoindolinones *via* a multicomponent reaction of 2-acetyl-oxirane-2-carboxamides, arylaldehydes and malononitrile†

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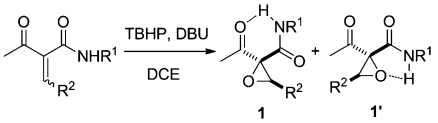
Efficient synthesis of spiro[isoquinolinone-4,2′-oxiranes] was achieved based on a multicomponent one-pot reaction of readily available *cis*-2-acetyl-oxirane-2-carboxamides, arylaldehydes and malononitrile at room temperature. However, in the reaction with *trans*-2-acetyl-oxirane-2-carboxamide substrates, 3-iminoisoindolinones were obtained in moderate to high yields.

Multicomponent reactions (MCRs) have been refined in recent years as powerful and useful tools in synthetic chemistry and have attracted increasing attention due to the advantages of greater efficiency, atom economy and structural complexity.[1] On the other hand, the utility of cyclopropane derivatives in organic chemistry has been recognized due to their "unsaturated" character.[2] In this context, the development of multicomponent reactions based on appropriately substituted cyclopropanes appears to be of significance and some studies have been reported by independent groups.[3] We have reported three-component reactions with highly functionalized 1-acetyl-1-carbamoyl cyclopropanes as the starting material.[3g,h] In the continued work, we started to explore the reaction based on electron-withdrawing groups-activated oxarines.[4] In the Knoevenagel reaction-initiated multicomponent reaction of 2-acetyl-oxirane-2-carboxamides, arylaldehydes and malononitrile, biologically important fused heterocycles 1*H*-spiro[isoquinoline-4,2′-oxiran]-3(2*H*)-ones and 3-iminoisoindolinones were synthesized with high efficiency. Isoquinolones constitute an important class of heterocyclic compounds, which displays important biological activities including vasorelaxation, cardiotonic effects and anticancer effects.[5] Isoindolinones contain the core found in many compounds in the heliannuol family of natural products.[6]



Scheme 1 Substrate preparation.

The substrates, 2-acetyl-oxirane-2-carboxamides, were prepared according to the literature reported procedure with slight modification.[7] Two regioisomers **1** and **1′** were easily isolated through column chromatography (Scheme 1).[8] The structure of 2-acetyl-*N*,3-diphenyloxirane-2-carboxamide (**1a′**) and the stereochemistry were confirmed by the X-ray single-crystal diffraction (Fig. 1). The different types of intramolecular hydrogen bonding in **1** and **1′** were established, which are supported by a distinctly different molecular polarity of **1** and **1′**, comparison of their ^{1}H NMR spectra and the X-ray single-crystal structure of **1′**.[9]

With substrates **1** and **1′** in hand, a multicomponent reaction of *cis*-2-acetyl-oxirane-2-carboxamide **1a**, benzaldehyde and malononitrile was conducted first (Table 1). Using K_2CO_3 (2.2 equiv.) as the base and DCM as the solvent, no reaction was observed (entry 1). When NaOH (2.2 equiv.) was used, product **3a** was obtained in 11% yield (entry 2). The structure of **3a** was confirmed unambiguously by X-ray single crystal diffraction (Fig. 2). DBU (2.2 equiv.) gave an increased yield of 35% (entry 3). To our delight, in the reaction using piperidine (2.2 equiv.) as the base in DCM at room temperature for only 1 h, the yield of **3a** reached up to 83% (entry 4). Other solvents tested like MeCN, THF and DMF were not as effective as DCM (entries 5–7). 1.1 equiv. of piperidine led to a decreased yield of 45% (entry 8).

Under the optimal conditions established above (Table 1, entry 4), a range of reactions was carried out with various substrates **1**,

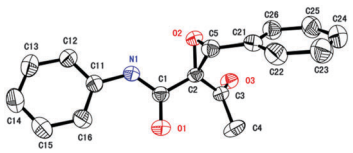


Fig. 1 X-ray crystal structure of **1a′**.

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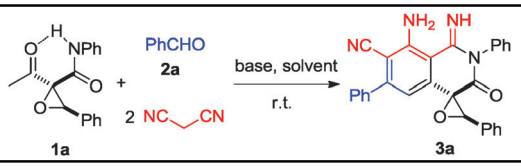
† Electronic supplementary information (ESI) available: Experimental details and characterization for all new compounds and crystal structure data. CCDC 971864 (**1a′**), 965575 (**3a**) and 977863 (**4a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc02141j

Table 1 Optimization of the reaction conditions



Entry	Base (2.2 equiv.)	Solvent	Time (h)	Yield[a] (%)
1	K_2CO_3	DCM	24	Nr
2	NaOH	DCM	24	11
3	DBU	DCM	24	35
4	**Piperidine**	**DCM**	**1**	**83**
5	Piperidine	MeCN	1	70
6	Piperidine	THF	1	45
7	Piperidine	DMF	1	10
8	Piperidine[b]	DCM	1	45

[a] Isolated yields. [b] 1.1 equiv. of piperidine.

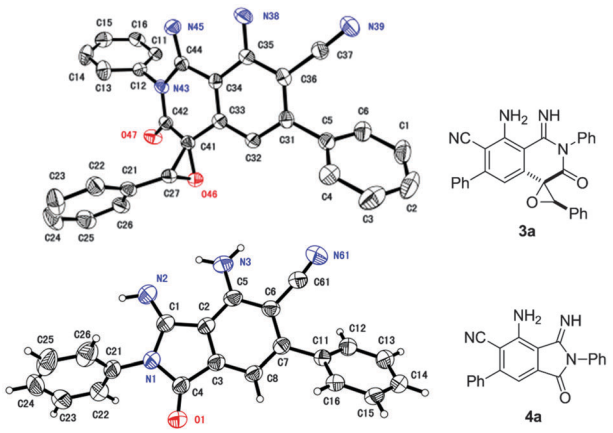


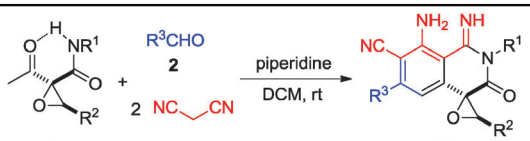
Fig. 2 X-ray crystal structures of **3a** and **4a**.

aldehydes and malononitrile (Table 2). The reactions proceeded smoothly to afford the corresponding highly substituted 1*H*-spiro-[isoquinoline-4,2′-oxiran]-3(2*H*)-ones **3** in moderate to high yields.[10] The R^1 substituents on the *N* atom of substrates **1** may be either aryls such as phenyl, 4-chlorophenyl and 4-methylphenyl (entries 1–3) or alkyls such as benzyl (entry 4). The R^2 substituents on the cyclopropyl ring of substrates **1** included phenyl, 4-methylphenyl, 4-bromophenyl and 4-pyridyl (entries 1, 5–7). The scope of aldehydes **2** was also examined.[11] Both electron-rich and electron-poor arylaldehydes (entries 8–13) and an heteroarylaldehyde (entry 14) gave good results.

In the following work, *trans*-2-acetyl-oxirane-2-carboxamides (**1′**) were subjected to the multi-component reaction with aryl-aldehydes and malononitrile (Table 3). However, in this case, 1*H*-spiro[isoquinoline-4,2′-oxiran]-3(2*H*)-ones **3** were not obtained. Instead, isoindolinones **4** were isolated after the reaction proceeded at room temperature for 48 h.[12] The structure of **4a** was confirmed by X-ray single crystal diffraction (Fig. 2). The yields were higher when DBU was used as the base to replace piperidine, affording **4a–h** in 48–85% yields (entries 1–9).[13]

In an isolated reaction of **1a′** with phenylaldehyde and malononitrile, intermediate **5** could be separated in 86% yield when the reaction proceeded for 0.5 h and quenched by

Table 2 Reaction of *cis*-2-acetyl-oxirane-2-carboxamides (**1**), aldehydes and malononitrile leading to 1*H*-spiro[isoquinoline-4,2′-oxiran]-3(2*H*)-ones **3**[a]



Entry	R^1	R^2	R^3	3	Yield[b] (%)
1	Ph	Ph	Ph	**3a**	83
2	4-MeC_6H_4	Ph	Ph	**3b**	74
3	4-ClC_6H_4	Ph	Ph	**3c**	68
4	Bn	Ph	Ph	**3d**	70
5	Ph	4-MeC_6H_4	Ph	**3e**	80
6	Ph	4-BrC_6H_4	Ph	**3f**	73
7	Ph	4-Pyridyl	Ph	**3g**	72
8	Ph	Ph	4-MeC_6H_4	**3h**	67
9	Ph	Ph	4-$MeOC_6H_4$	**3i**	69
10	Ph	Ph	2-$MeOC_6H_4$	**3j**	66
11	Ph	Ph	4-ClC_6H_4	**3k**	77
12	Ph	Ph	4-BrC_6H_4	**3l**	78
13	Ph	Ph	3-$NO_2C_6H_4$	**3m**	73
14	Ph	Ph	2-Thienyl	**3n**	71

[a] Reactions were carried out with **1** (1.0 mmol), **2** (1.1 equiv.), malononitrile (2.2 equiv.), piperidine (2.2 equiv.) in CH_2Cl_2 (4.0 mL) at room temperature for around 1 h. [b] Isolated yield.

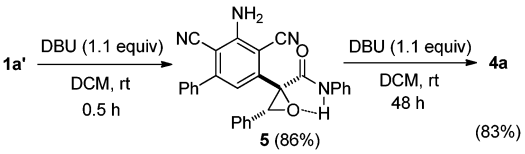
Table 3 Reaction of *trans*-2-acetyl-oxirane-2-carboxamides (**1′**), aryl-aldehydes and malononitrile leading to isoindolinones **4**[a]

Entry	R^1	R^2	Ar	4	Yield[b] (%)
1	Ph	Ph	Ph	**4a**	85
2	4-MeC_6H_4	Ph	Ph	**4b**	79
3	4-ClC_6H_4	Ph	Ph	**4c**	61
4	Ph	4-BrC_6H_4	Ph	**4a**	80
5	Ph	4-Pyridyl	Ph	**4a**	71
6	Ph	Ph	4-MeC_6H_4	**4d**	48
7	Ph	Ph	4-FC_6H_4	**4e**	66
8	Ph	Ph	4-ClC_6H_4	**4f**	75
9	Ph	Ph	4-BrC_6H_4	**4g**	77
10	Ph	Ph	2-Thienyl	**4h**	70

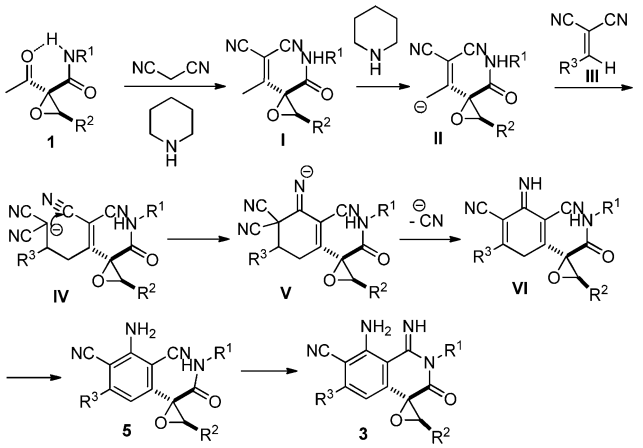
[a] Reactions were carried out with **1** (1.0 mmol), **2** (1.1 equiv.), malononitrile (2.2 equiv.), DBU (1.1 equiv.) in CH_2Cl_2 (4.0 mL) at room temperature for 48 h. [b] Isolated yield.

water (Scheme 2). Intermediate **5** could be further converted into **4a** in 83% yield in 48 h at room temperature.

Based on all the above results, along with the previous work by Ge and Li[14a] and Yan,[14b,c] a possible mechanism for the formation of 1*H*-spiro[isoquinoline-4,2′-oxiran]-3-ones **3** has been proposed in Scheme 3. The process involves tandem Knoevenagel condensation,



Scheme 2 Control experiment.



Scheme 3 Plausible mechanism for the formation of 1*H*-spiro[isoquinoline-4,2′-oxiran]-3-ones **3**.

intermolecular Michael addition, intramolecular carbo-cyclization (to form the six-membered carbon ring), aromatization *via* elimination of the cyanide anion and intramolecular aza-cyclization (to form the six-membered nitrogen ring). The mechanism for the formation of isoindolinones **4** is not clear.[15]

In conclusion, room-temperature multicomponent reactions based on 2-acetyl-oxirane-2-carboxamides, arylaldehydes and malononitrile have been developed. Depending on the different intramolecular hydrogen bonding modes in 2-acetyl-oxirane-2-carboxamide substrates, reactions with *cis*-2-acetyl-oxirane-2-carboxamides afford 1*H*-spiro[isoquinoline-4,2′-oxiran]-3(2*H*)-ones in a short time (around 1 h). Upon reaction with *trans*-2-acetyl-oxirane-2-carboxamides, 3-iminoisoindolinones were obtained in 48 h. Further work on the application of highly functionalized oxarines in organic synthesis is ongoing.

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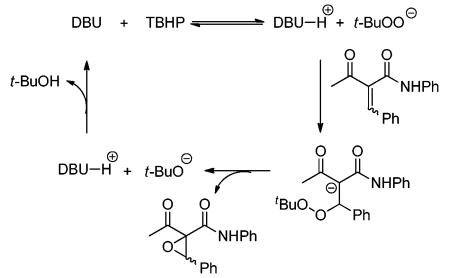
8 No matter (*Z*)- or (*E*)-2-benzylidene-3-oxo-*N*-phenylbutanamides can furnish compounds **1** and **1′** (possible mechanism as below). The ratio of **1** and **1′** are independent on the *Z*,*E*-ratio of 2-benzylidene-3-oxo-*N*-phenylbutanamides.



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10 No fragmentation of the oxirane moiety was observed even the reaction proceeded at room temperature for 48 h.

11 When alkylaldehyde like *n*-butylaldehyde was used, no target molecule was observed.

12 For selected examples on the reactivity of substituted oxarines, see: (*a*) H. Liao and R. Liu, *Chem. Commun.*, 2011, **47**, 1339; (*b*) C. Yang, M. Lin, H. Liao and R. Liu, *Chem. – Eur. J.*, 2010, **16**, 2696; (*c*) M. Wang, S. Lin, C. Liu, Q. Zheng and J. Li, *J. Org. Chem.*, 2003, **68**, 4571; (*d*) L. Yang, G. Deng, D. Wang, Z. Huang, J. Zhu and M. Wang, *Org. Lett.*, 2007, **9**, 1387.

13 Reaction of 2-acetyl-*N*-benzyl-3-phenyloxirane-2-carboxamide with phenylaldehyde and malononitrile afforded multisubstituted benzene with the structure of type **5**.

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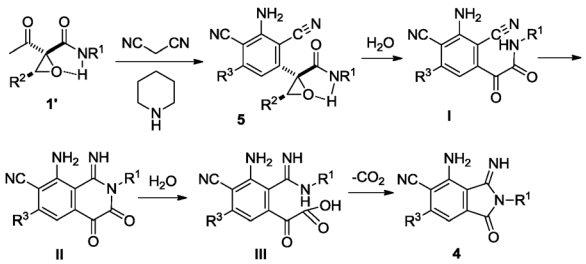
15 A plausible mechanism was given as below. Firstly, intermediate **5** would be generated (details see Scheme 3), which does not undergo aza-cyclization with the cyano group to give fused heterocycle of type **3**, mainly due to the intramolecular hydrogen bond of amide group with the oxarine oxygen atom. Then, the fragmentation of the oxarine takes place within 48 h, giving α-oxoamide **I**. In this case, aza-cyclization becomes possible and bicyclic **II** is formed. Finally, product **4** is supposed to be generated *via* sequential hydrolysis of α-oxoamide, decarboxylation and recyclization (**II** → **III** → **4**).



It was noteworthy that arylaldehyde side product, R^2CHO, could be observed in the reaction system.