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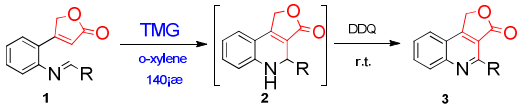

The first TMG catalyzed intramolecular aza-MBH reaction based on furanone derivatives for the construction of furo[3,4-c]quinolin-3(1H)-ones scaffold

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ARTICLE TYPE

Synthesis of furo[3,4-c]quinolin-3(1*H*)-one derivatives through TMG Catalyzed Intramolecular aza-MBH Reaction based on the furanones

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The first TMG catalyzed intramolecular aza-MBH reaction based on furanone derivatives was developed and successfully applied in the synthesis of a novel fused heterocyclic scaffold, furo[3,4-c]quinolin-3(1*H*)-ones in moderate to good yields.

The 2(5*H*)-furanone structural motif is found in a number of natural products which exhibits a wide range of biological activities, including antifungal, antibacterial, antiprotozoal, anti-cancer, anti-virus, anti-inflammatory, and so on (Fig. 1).[1,2] Quinoline is one of the most prevalent scaffolds encountered in medicinal chemistry.[3] For example, there are four drugs with quinolone scaffold among twenty eight NCEs newly approved by the U.S. Food and Drug Administration (FDA) in 2012 (Fig. 2).[4] Thus, we envisaged the combination of quinoline derivatives with 2(5*H*)-furanone moiety which would lead to a new kind of scaffold with potential biological activity. However, there is only one patent involving the synthesis of such kind of compounds, in which the author used harsh conditions and multi-step reaction. (US005604235) Therefore, the need for the development of more convenient methods remains.

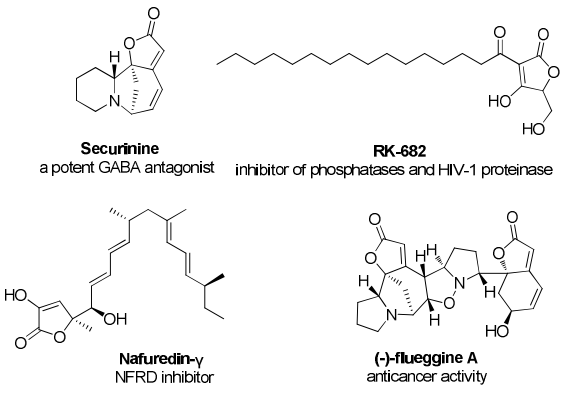
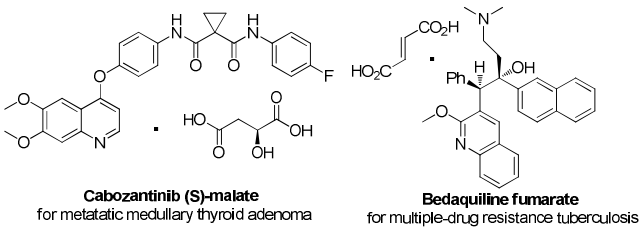


Fig. 1 Representative products containing 2(5*H*)-furanone scaffold



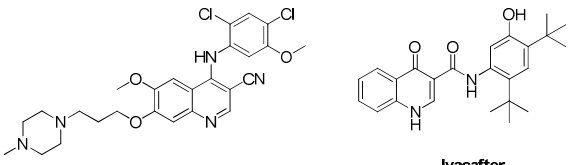
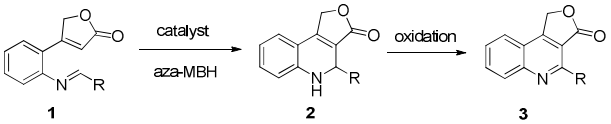


Fig. 2 Structures of NCEs containing quinoline scaffold marketed/approved in 2012 by FDA.

The Morita-Baylis–Hillman (MBH) reaction is one of the most useful and popular carbon−carbon bond forming reactions since its atom economy and functional group generation.[5] Over the last two decades, this reaction and its applications have received remarkably growing interest. However, comparing with the intermolecular Morita-Baylis-Hillman (MBH) reaction,[6] the intramolecular MBH reaction is still not fruitful.[7] As a continuation of our ongoing effort in developing the reactions based on 2(5*H*)-furanone,[8] we herein disclose the first tetramethyl guanidine (TMG) catalyzed intramolecular aza-MBH reaction of 2(5*H*)-furanone derivatives **1** to construct the key intermediate dihydrofuro[3,4-c] quinolin-3(1*H*)-ones **2**, which was easily transformed into furo[3,4-c] quinolin-3(1*H*)-one derivatives **3** by oxidation(Scheme 1).



Scheme 1

At the beginning of our study, the starting materials **1** were conveniently obtained according to the method reported by Patel (Detailed information shown in supporting information).[9] Then, 4-(2-(benzylideneamino)phenyl)furan-2(5H)-one (**1a**) was chosen as model substrate to optimize the reaction conditions for intramolecular aza-MBH reaction. Various catalysts, including organic bases and Lewis acids which are commonly used in the MBH reaction, were firstly screened. As shown in Table 1, only two non-nuclephilic organic bases, DBU and TMG, gave the desired product dihydrofuro[3,4-c] quinolin-3(1*H*)-one **2a** in low yields of 11% and 19%, respectively (Entries 7 and 8, Table 1). Much to our delight, when using TMG as the catalyst and increasing the reaction temperature, the yield was greatly improved and the reaction time was significantly shortened. When the reaction was carried out at 120°C, compound **2a** was obtained in

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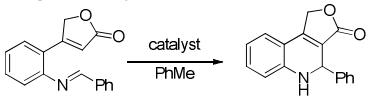
63% yield in 20h (Entry 10, Table 1). However, it is noteworthy that compound **2a** was vulnerable to oxidation even under room temperature and DDQ could oxidize **2a** to furo[3,4-c] quinolin-3(1*H*)-one **3a** quantitively within 5 minutes. Considering the unstability, compounds **2** were directly oxidized to **3** in the subsequent study. Encouraged by this promising finding, we continued to explore the influence of other high boiling point solvents on the reaction, which included o-xylene, ethylene glycol, diethylene glycol, N-methyl-2-pyrrolidone (NMP) and n-octane (Entries 1-5, Table 2). The results reveal that o-xylene is the best choice for the improvement of yields and shorten of reaction time (Entry 5, Table 2). Furthermore, the screening of catalyst loading reveals that lower catalyst loading was unfavourable for the reaction (Entries 6-7, Table 2). Thus, 20mol% of TMG catalyst, o-xylene as solvent and 140°C were chosen to be the most suitable reaction conditions.

Table 1 Screening of catalysts.

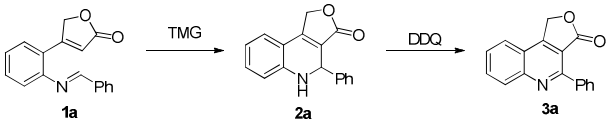


1a 2a

Entry.	Catalyst	Temp.(℃)	time	yield[a]
1	Triethylamine 20mol%	50	48h	Trace
2	DIPEA 20mol%	50	48h	Trace
3	DABCO 20mol%	50	48h	Trace
4	TMEDA 20mol%	50	48h	Trace
5	CuTc 20mol%	50	48h	N.R.
6	$ZnCl_2$20mol%	50	48h	N.R.
7	DBU 20mol%	50	48h	11%
8	TMG 20mol%	50	48h	19%
9	TMG 20mol%	100	24h	34%
10	TMG 20mol%	120	20h	63%

[a] Isolated yields by silica-gel column purification.

Table 2 Screening of solvent, temperature and catalyst loading.



1a 2a 3a

Entry	Catalyst	Solvent	Temp.(°C)	Time	Yield[a]
1	TMG 20mol%	Diethylene Glycol	140	1h	29%
2	TMG 20mol%	Ethylene Glycol	140	2h	19%
3	TMG 20mol%	NMP	140	2h	42%
4	TMG 20mol%	n-Octane	140	2h	11%
5	TMG 20mol%	o-Xylene	140	7h	69%
6	TMG 10mol%	o-Xylene	140	24h	47%
7	TMG 5mol%	o-Xylene	140	24h	31%

[a] Overall yield after DDQ oxidation.

With the optimal reaction conditions in hand, the scope of the reaction was explored. In most cases, the reactions proceeded smoothly to generate furo[3,4-c] quinolin-3(1*H*)-one **3** in moderate to good yields. For imines **1** derived from substituted aromatic aldehydes, both the position and the properties of substituted group would affect the yield of aza-MBH reaction. Usually, electron donating substituents afforded good yields (yields from 64%-75%, **1b-1f**) except the one with para-methoxy group whose strong donating effect may reduce the electrophilicity of imine carbon. Simultaneously, electron withdrawing substituents also afforded the acceptable results (yields 40%-53%, 1g-1j). Besides, the substrates from heterocyclic aromatic aldehydes (1l-1o) and aliphatic aldehydes (1p, 1q) could yield the reaction and provide the corresponding aza-MBH products. To further expand the substrate scope of this methodology, we turned our attention to the substrates derived from cinnamaldehyde and its derivatives. Much to our surprise, under optimized reaction conditions, these substrates afforded the products 4-phenethylfuro[3,4-c]quinolin-3(1H)-ones (3r'-3t') instead of the expected product 4-styrylfuro[3,4-c]quinolin-3(1H)-ones (3r-3t) (Fig 4), suggesting that the final aromatization step was derived from hydrogen migration rather than DDQ oxidation. This proposal was supported by the experimental result that the product (**3r'**) was also obtained by stirring the intermediate compound **2r** in 5% p-toluene sulfonic acid (PSA) overnight under argon atmosphere.

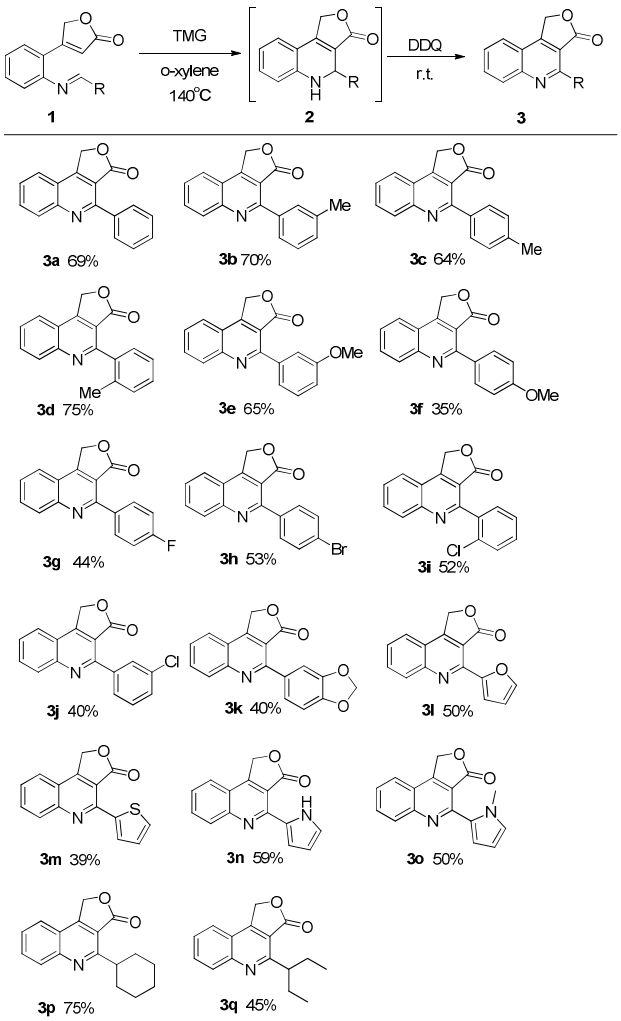


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Fig. 3 Substrate scope of intramolecular aza-MBH reaction

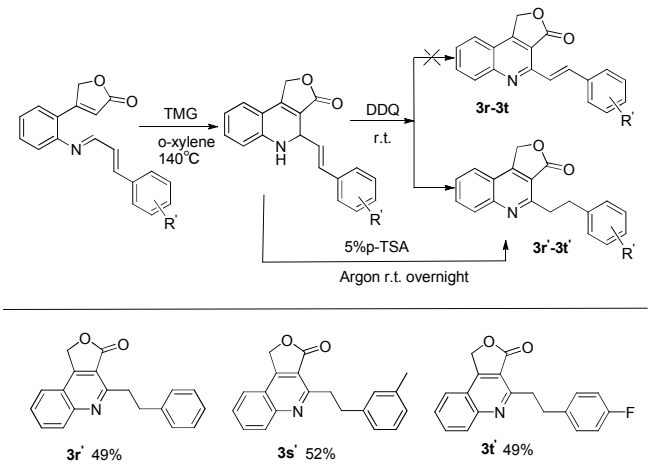
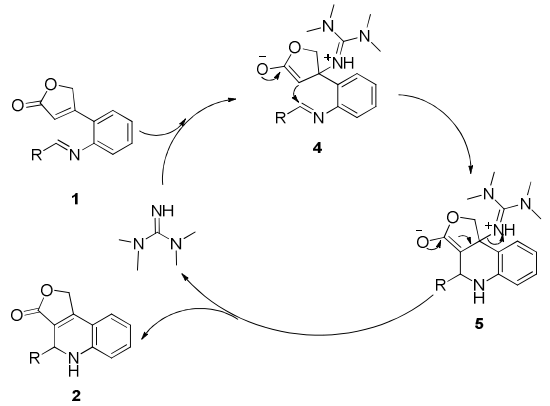


Fig. 4 Substrate scope of intramolecular aza-MBH reaction

According to the literature,[10] a possible mechanism of this intramolecular aza-MBH reaction is proposed in Scheme 2. Through 1,4-addition reaction, TMG attacks the activated alkene **1** to generate the zwitterionic aza-enolate **4**. Then **4** undergoes the intramolecular aldol-like reaction affording the cyclized intermediate **5**. Finally, releasing TMG from **5** yields the product **2**.



Scheme 2 Plausible mechanism for the intramolecular aza-MBH reaction.

Conclusions

In summary, we have developed the first TMG catalyzed intramolecular aza-MBH reaction based on the furanone derivatives and a novel series of furo[3,4-*c*] quinolin-3(1*H*)-one derivatives were synthesized in moderate to good overall yields. This reaction could tolerate a wide range of substituents including aryl, heterocyclic aryl, alkyl and vinyl groups. Furo[3,4-c] quinolin-3(1*H*)-one represents a new kind of fused heterocyclic scaffold containing furanone and quinoline, which would become a more potential privileged structure in the drug discovery.

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Notes and references

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