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# Free radical reactions for heterocycle synthesis. Part 3: Formation of novel spirodilactones, spirolactone-lactams, and spirolactone-thiolactones[1]

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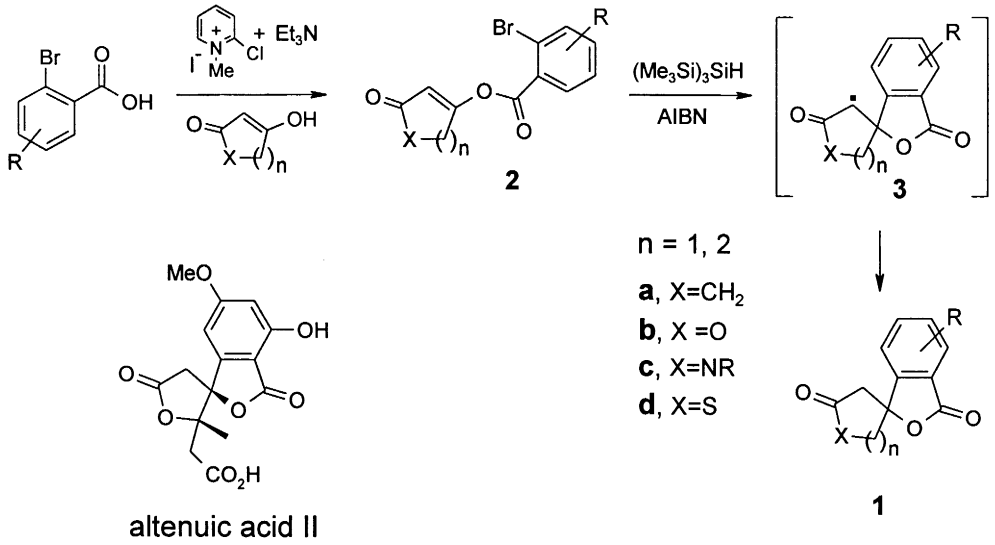
**Abstract**

Synthesis of spirodilactones is achieved by intramolecular free radical Michael addition of enol esters derivatized from tetronic acid. Synthesis of spirolactone-lactams and spirolactone-thiolactones is also covered by the scope of this new reaction. 

We recently reported a new method for synthesis of keto spiro-γ-lactones **1a** based on intramolecular free radical Michael addition (Scheme 1).[1b] Regioselective 5-*exo* cyclization of aryl radicals generated from enol esters **2a** led to formation of a spiro-quaternary carbon bond of **3a**. Formation of stabilized




Scheme 1.

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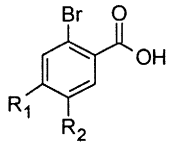
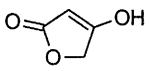
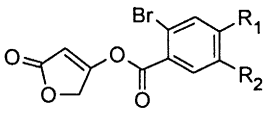
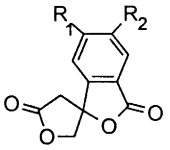
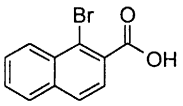
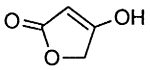
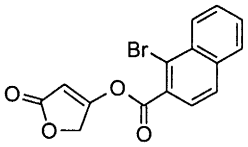
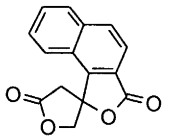
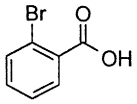
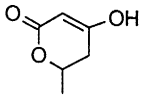
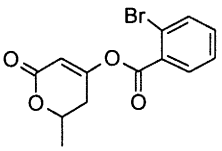
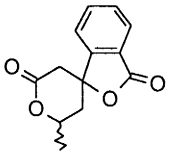
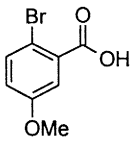
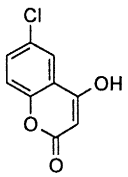
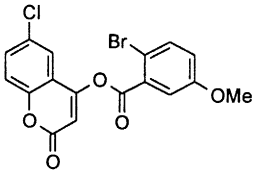
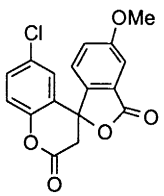
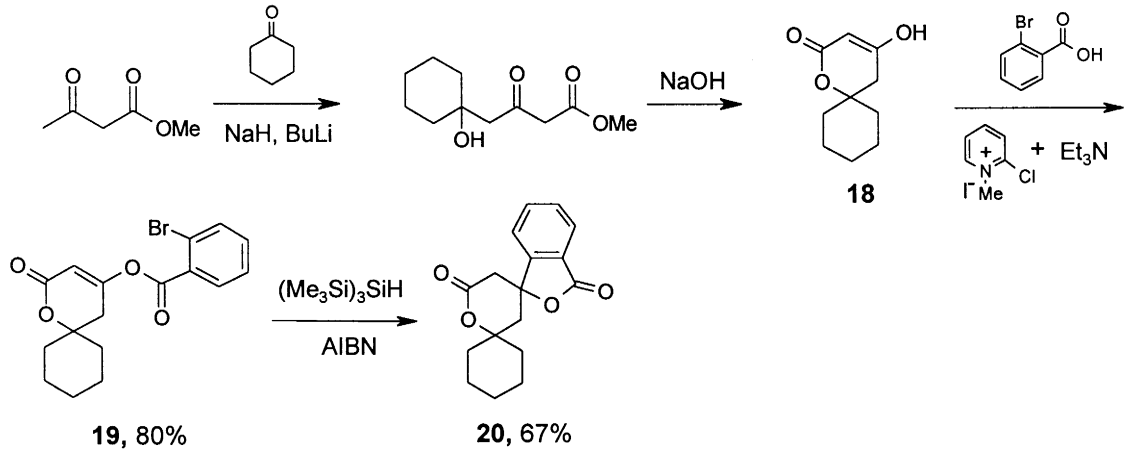
intermediate radicals **3a** facilitates the spirocyclization process. This method is now extended to the synthesis of novel spirodilactones **1b**, spirolactone-lactams **1c**, and spirolactone-thiolactones **1d**.

Spirodilactones **1b** (*n*=1) possess a rare heterocyclic system which is found in natural product altenuic acid II.[2] To my knowledge, no synthetic method for spirodilactones **1b** is available in the literature. Using the new method, we can easily accomplish the synthesis of spirodilactones. Thus, free radical cyclization of **2b** in refluxing benzene using 1.5 equiv. of tris(trimethylsilyl)silane and catalytic amount of 2,2′-azobis(2-methylpropionitrile) (AIBN) as initiator gave spirodilactones **1b** in 50–87% yield (Table 1).[3] Direct reduction product, which is a common byproduct associated with reductive radical reaction using tributyltin hydride or tris(trimethylsilyl)silane, was not observed. Radical precursors, enol esters **2b**, were prepared by coupling of 2-bromobenzoic acids with tetronic acid in the presence of 1.2 equiv. of 2-chloro-1-methylpyridinium iodide and 2.4 equiv. of triethylamine in THF at room temperature.

Table 1
Preparation of spirodilactones[3]

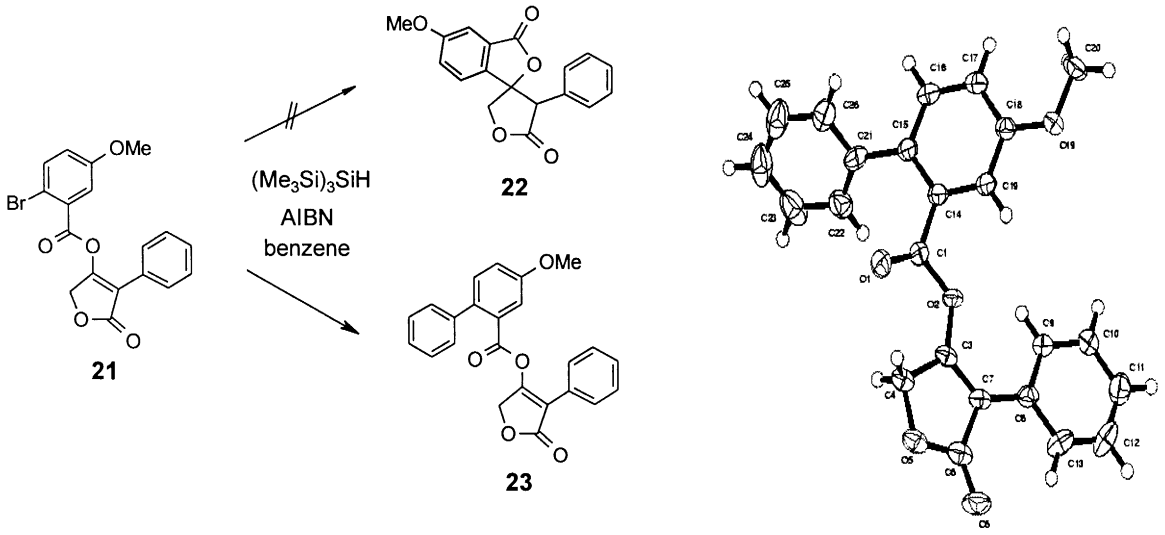
| entry | substrates | | enol ester | product |
|---|---|---|---|---|
| 1 |  |  |  |  |
| | | | $R_1$, $R_2$=H, **4,** 83%<br>$R_1$=H, $R_2$=OMe, **6,** 83%<br>$R_1$, $R_2$=OMe, **8,** 47% | $R_1$, $R_2$=H, **5,** 75%<br>$R_1$=H, $R_2$=OMe, **7,** 50%<br>$R_1$, $R_2$=OMe, **9,** 76% |
| **2** |  |  |  |  |
| | | | **10,** 100% | **11,** 87% |
| **3** |  |  |  |  |
| | | **12** | **13,** 90% | **14** (1:1.2), 70% |
| **4** |  |  |  |  |
| | | **15** | **16,** 94% | **17**, 74% |



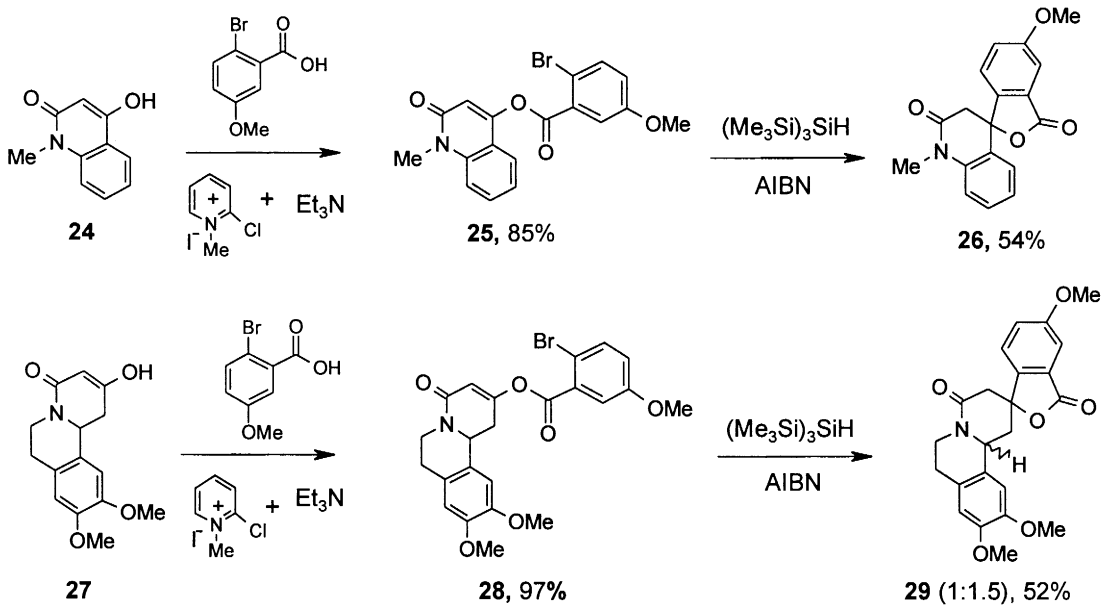

Scheme 2.

Examples listed in Table 1 illustrate the scope of spirodilactone synthesis. Entry 1 demonstrates the preparation of spirodi-ɣ-lactones which have different substituents on the benzene ring. Purification of both the intermediate enol esters **4**, **6** and **8** and the corresponding cyclization products **5**, **7** and **9** was straightforward; they can be simply precipitated out from the concentrated reaction mixture at room temperature. In entry 2, 1-bromo-2-naphthoic acid was coupled with tetronic acid to form enol ester **10** which then underwent naphthyl radical cyclization to form tetracyclic spirodi-ɣ-lactone **11**. The use of 5,6-dihydro-4-hydroxy-6-methyl-2*H*-pyran-2-one (**12**) instead of tetronic acid led to formation of spiro-ɣ/δ-dilactone **14** as a mixture of diastereomers (entry 3). Entry 4 provides another example for synthesis of tetracyclic spiro-ɣ/δ-dilactone **17**. Scheme 2 demonstrates the synthesis of spiro dihydropyranone **18**[4] which led to formation of dispiro-ɣ/δ-dilactone **20** as a single diastereomer.

To study the substitution effect, cyclization of enol ester **21** derivatized from 3-phenyl tetronic acid was attempted (Scheme 3). Probably because of steric hindrance of the 3-phenyl group on the tetronic acid ring, no desired cyclization product **22** was observed. Surprisingly, a solvent (benzene) coupling product **23** (15%) was isolated from the complex reaction mixture and its structure was characterized by X-ray analysis (Scheme 3).




Scheme 3. Formation of **23** and its X-ray structure

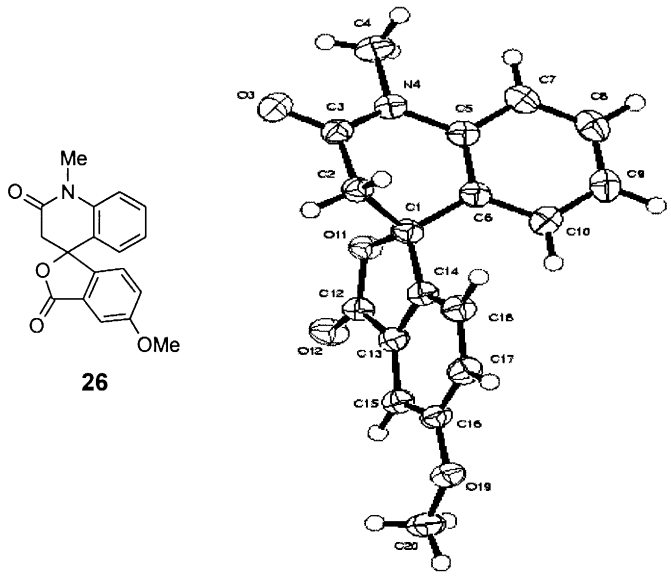



Scheme 4.

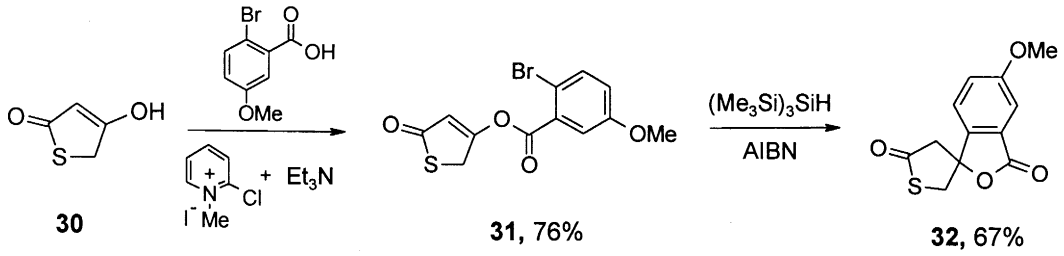
Free radical spirorization reaction has been successfully used to synthesize spirolactone-lactams **26** and **29** (Scheme 4) starting from commercially available lactam **24** and readily available lactam **27**.[5] Both cyclization products have functionalized polycyclic systems. The structure of product **26** was confirmed by X-ray crystal analysis (Scheme 5).

Free radical spirorization reaction has been further applied to the synthesis of spirolactone-thiolactone **32** using commercially available thiotetronic acid (**30**) as starting material (Scheme 6).

In summary, a general spirocyclization process has been developed for the synthesis of a series of novel spirodilactone, spirolactone-lactam and spirolactone-thiolactone compounds. This method is believed to




Scheme 5. X-Ray structure of compound **26**




Scheme 6.

have great potential in the preparation of biologically interesting spiro heterocycles. Work aimed at total synthesis of altenuic acid II is currently underway and will be reported in due course.

## Acknowledgements

The author thanks William Marshall for X-ray structural analysis of compounds **23** and **26**.

## References

1. Papers 1 and 2 in this series: (a) Zhang, W.; Pugh, G. *Tetrahedron Lett*. **1999**, *40*, 7591. (b) Zhang, W.; Pugh, G. *Tetrahedron Lett*. **1999**, *40*, 7595.
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