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Free radical reactions for heterocycle synthesis: formation of keto spiro-γ-lactones and keto spiro-γ-lactams †

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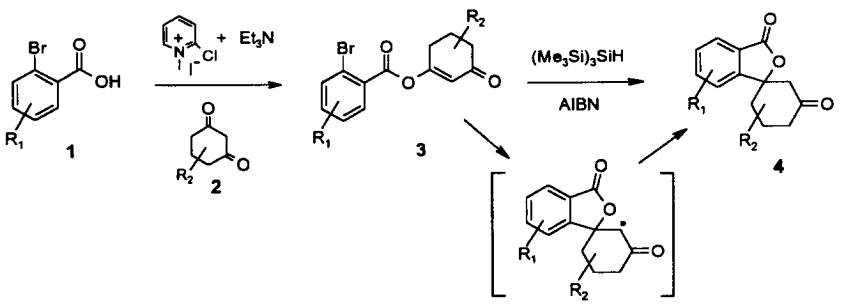
Abstract

A new method for the synthesis of keto spiro-γ-lactones and keto spiro-γ-lactams by intramolecular free radical cyclization is described. © 1999 Elsevier Science Ltd. All rights reserved.

There is extensive literature discussing the synthesis of spirolactones[1] because of their unique molecular structure and interesting biological activity. In the development of new methods for the preparation of novel heterocyclic compounds, we have discovered a simple method for the synthesis of keto spiro-γ-lactones and keto spiro-γ-lactams based on free radical cyclizations.



(1)

The new approach is a two-step synthesis (Eq. 1): formation of enol esters **3** by coupling of a halogenated carboxylic acid **1** with a 1,3-cyclic dione **2** followed by a $(CH_3Si)_3SiH$ promoted free radical cyclization[2] to produce keto spiro-γ-lactones **4**. Examples listed in Table 1 illustrate the synthetic scope of this method. Yields for both the coupling and free radical cyclization steps are good.

Starting materials, including halogenated carboxylic acids **1** and 1,3-cyclohexanediones **2**, are commercially available. 1,3-Cycloheptanedione was prepared by a reported procedure.[3] Free radical cyclization of 5-phenyl substituted 1,3-cyclohexanedione derivatives (Table 1, entries 2–5) gave products **18** and

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† In memory of Professor Paul Dowd.

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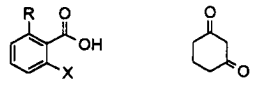
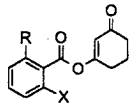
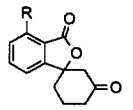
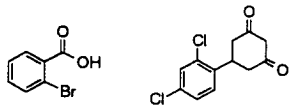
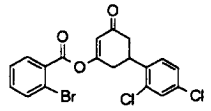
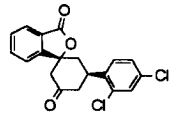
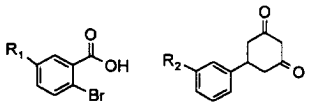
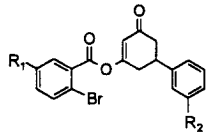
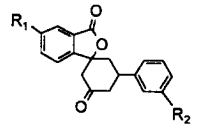
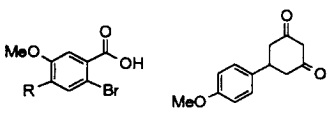
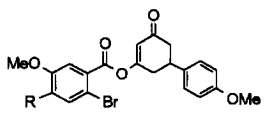
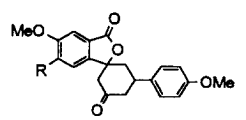
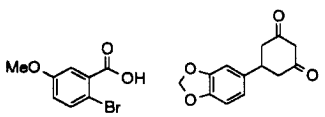
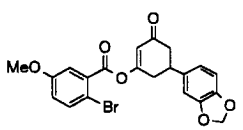
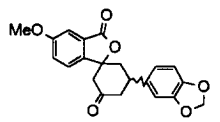
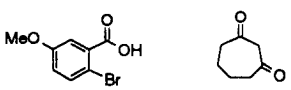
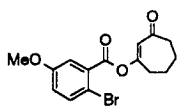
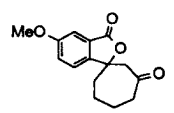
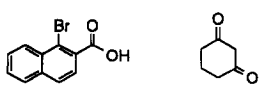
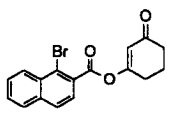
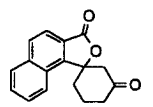
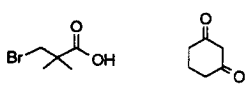
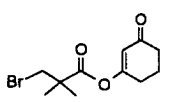
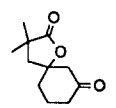
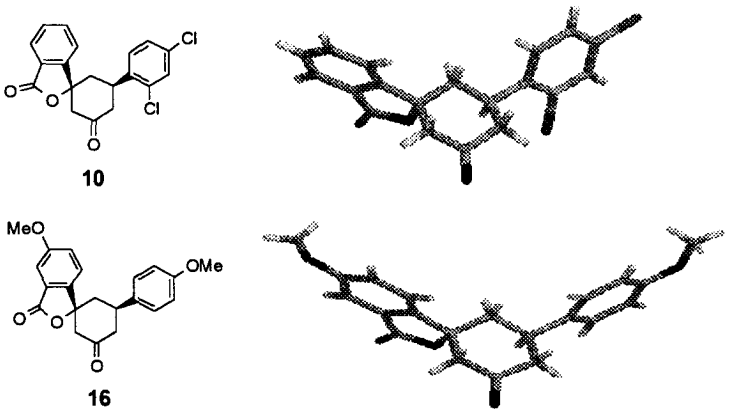
Table 1
Preparation of keto spiro-γ-lactones[4]

entry	substrates	enol ester	product
1		 R=H, X=Br, **5**, 99% R=F, X=I, **7**, 89%	 R=H, **6**, 83% R=F, **8**, 68%
2		 **9**, 70%	 **10**, 68%
3		 R_1=H, R_2=Cl, **11**, 88% R_1=OMe, R_2=CF_3, **13**, 68%	 R_1=H, R_2=Cl, **12**, 76% R_1=OMe, R_2=CF_3, **14**, 64%
4		 R=H, **15**, 51% R=OMe, **17**, 84%	 R=H, **16**, 42% R=OMe, **18** (1:1 diast mix), 70%
5		 **19**, 100%	 **20/21** (1:3 diast mix), 56%
6		 **22**, 83%	 **23**, 76%
7		 **24**, 646%	 **25**, 60%
8		 **26**, 86%	 **27**, 76%

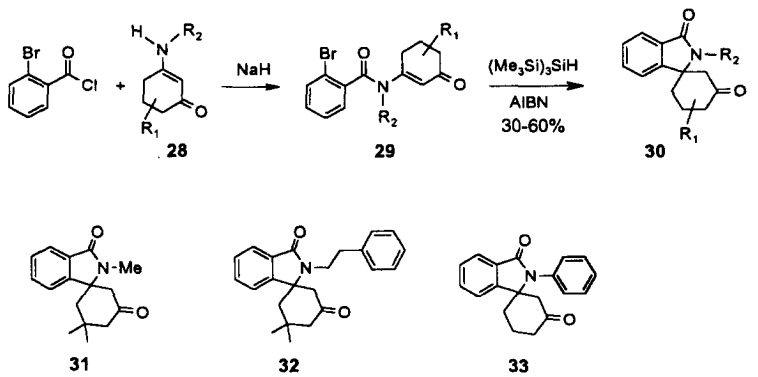
yield and ratio of diastereomers have not been optimized

20/21 as mixtures of diastereomer, respectively, while **10**, **12**, **14** and **16** were isolated from the reaction mixture as single diastereomer, respectively. The stereostructures of **10** and **16** were determined by X-ray analysis (Scheme 1).



Scheme 1. X-Ray structures of compounds **10** and **16**

Extension of this method for preparing keto spiro-γ-lactams, **31**, **32** and **33**, has been accomplished by coupling amines **28** with 2-bromobenzoyl chloride followed by free radical cyclization of amides **29** (Eq. 2).



(2)

Yields for the formation of keto spiro-γ-lactams were somewhat lower (30–60%) than those observed for keto spiro-γ-lactones (Table 1). Similar methods for making spirolactams based on Heck[5] or free radical reactions[6] are reported in the literature.

General procedure for the preparation of enol esters. Preparation of **5**: A mixture of 1.10 g (5.0 mmol) of 2-bromobenzoic acid, 1.50 g (5.5 mmol) of 1,3-cyclohexanedione, 1.50 g (5.8 mmol) of 2-chloro-1-methylpyridinium iodide, and 1.80 mL of triethylamine in 100 mL of anhydrous THF was stirred at room temperature overnight. TLC showed no starting material was present. The reaction mixture was concentrated to remove THF, followed by extraction with ethyl acetate. The combined organic layers were washed with NH_4Cl (aq.) and brine, dried over $MgSO_4$, and concentrated in vacuo to afford 1.47 g (99%) of enol ester **5** as a clear brown oil.

General procedure for the preparation of keto spiro-γ-lactones. Preparation of **6**: To a refluxing solution of 440 mg (1.5 mmol) of enol ester **5** in 36 mL of dry benzene was added 530 μL (1.8 mmol) of $(CH_3Si)_3SiH$ and 12 mg (0.07 mmol) of 2,2′-azobis(2-methylpropionitrile) (AIBN). After 2 h, another 12 mg of AIBN was added and reaction mixture was refluxed overnight. TLC showed the reaction was

complete. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (elution with 4:1, hexanes:ethyl acetate) to give 270 mg (83%) of keto spiro-γ-lactone **6** as a clear colorless oil.

Acknowledgements

We thank William Marshall and Dr. Dominic Chan for X-ray structural analysis.

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