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Free radical reactions for heterocycle synthesis: formation of tri- and tetracyclic isoindolinones

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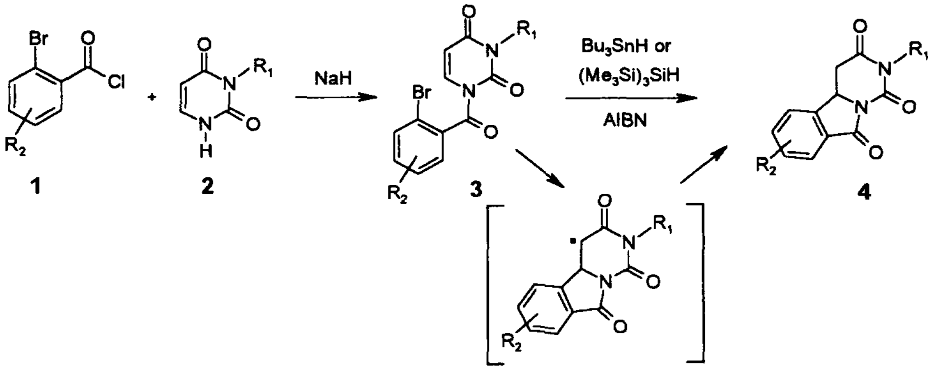
Abstract

A general method for synthesis of tri- and tetracyclic isoindolinones is achieved by intramolecular free radical cyclization. © 1999 Elsevier Science Ltd. All rights reserved.

Application of free radical reactions[1] in the synthesis of heterocycles[2] has attracted significant amounts of attention from the organic chemists. In our continuing efforts on the design and the development of new reactions,[3] we recently developed a general method for tri- and tetracyclic isoindolinone synthesis. Isoindolinones are a class of alkaloids possessing interesting biological activities.[4] A common method for isoindolinone construction is C–N bond formation via lactamization.[5] The C–C bond formation methods for isoindolinone synthesis based on the Heck[6] and free radical[7] reactions have been reported in the recent literature.



(1)

The method we report here for tri- and tetracyclic isoindolinone synthesis is very straightforward (Eq. 1). Free radical precursors **3** are readily prepared by *N*-acylation of a cyclic nitrogen compound **2**

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† In memory of Professor Paul Dowd.

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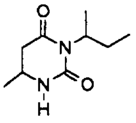
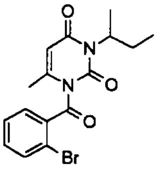
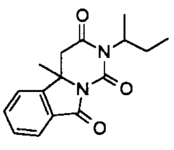
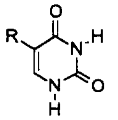
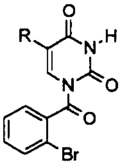
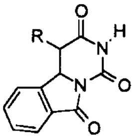
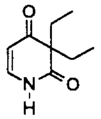
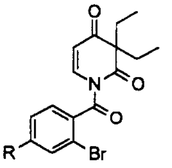
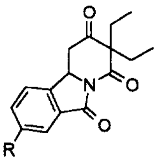
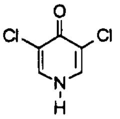
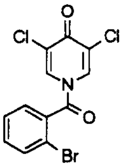
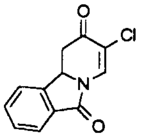
Table 1
Preparation of tricyclic isoindolinones[8]

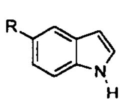
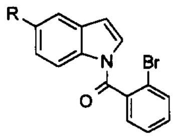
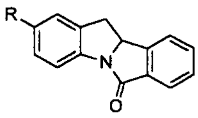
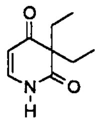
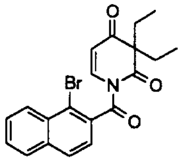
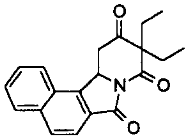
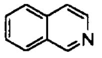
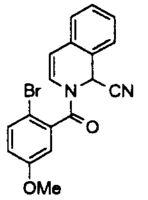
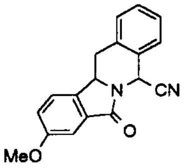
entry	substrate	radical precursor	product
1		 **5**, 80%	 **6**, 50%
2		 R=H, **7**, 46% R=CH_3, **9**, 49% R=CF_3, **11**, 52%	 R=H, **8**, 59% R=CH_3, **10**, 80% R=CF_3, **12**, 59%
3		 R= H, **13**, 62% R= OCH_3, **15**, 92%	 R= H, **14**, 53% R= OCH_3, **16**, 71%
4		 **17**, 98%	 **18**, 43%

with a 2-bromobenzoyl chloride **1** in the presence of NaH or pyridine as a base. Free radical reactions promoted by Bu_3SnH or $(CH_3Si)_3SiH$ using a catalytic amount of AIBN as initiator give cyclization products **4** in good yield.

Examples listed in Table 1 illustrate the synthesis of tricyclic isoindolinones using commercially available cyclic nitrogen compounds as starting materials, including uracils (Table 1, entries 1 and 2), 3,3-diethyl-2,4(1*H*,3*H*)-pyridinedione (Table 1, entry 3), and 3,5-dichloro-4-pyridone (Table 1, entry 4). Uncapped uracils can be selectively acylated at the 1-N position using pyridine as a base (Table 1, entry 2). Radical cyclization products **8**, **10**, and **12** can be further functionalized at the position of uncapped nitrogen.

Following a similar procedure described for tricyclic isoindolinone synthesis, several tetracyclic isoindolinones were prepared (Table 2) starting with indoles (Table 2, entry 1), 3,3-diethyl-2,4(1*H*,3*H*)-

Table 2
Preparation of tetracyclic isoindolinones[8]

entry	substrate	radical precursor	product
1		 R= H, **19**, 80% R= OCH_2Ph, **21**, 68%	 R= H, **20**, 53% R= OCH_2Ph, **22**, 71%
2		 **23**, 67%	 **24**, 77%
3		 **25**, 35% (ref. 9)	 **26**, 59%

pyridinedione (Table 2, entry 2), and isoquinoline (Table 2, entry 3).[9] Compound **24** is a product of naphthyl radical cyclization. Product **26** was isolated as a single isomer, its stereostructure has not been determined yet.

General *N*-acylation procedure. Preparation of **15**: To a suspension of 300 mg of NaH (60% in mineral oil, 7.2 mmol) in 5 mL of anhydrous THF was added a solution of 1.0 g (6 mmol) of 3,3-diethyl-2,4(1*H*,3*H*)-pyridinedione in 15 mL of anhydrous THF at room temperature. After being stirred for 45 min, 1.8 g (7.2 mmol) of 2-bromo-5-methoxybenzoyl chloride was added dropwise. The reaction mixture was stirred at room temperature overnight. TLC showed no starting material was present. The reaction was quenched with ice and extracted 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 2.1 g (92%) of *N*-acylation product **15** as a semisolid.

General free radical cyclization procedure. Preparation of **16**: To a refluxing solution of 1.0 g (2.6 mmol) of bromide **15** in 50 mL of dry benzene was added 980 µL (3.2 mmol) of $(CH_3Si)_3SiH$ and 20 mg (0.15 mmol) of 2,2′-azobis(2-methylpropionitrile) (AIBN). After 2 h, another 20 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. Trituration of crude product with 1-chlorobutane gave 560 mg (71%) of cyclization product **16** as white solid.

Acknowledgements

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