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Smooth Isoindolinone Formation from Isopropyl Carbamates via Bischler−Napieralski-Type Cyclization

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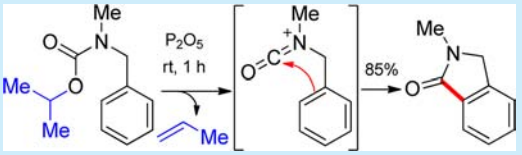
Supporting Information

ABSTRACT: Isopropyl carbamates derived from benzylamines provide isoindolinones by treatment with phosphorus pentoxide at room temperature. Utility of this Bischler−Napieralski-type cyclization and a new mechanism involving a carbamoyl cation for rationalization of this smooth conversion are discussed.



Isoindolinone skeletons are frequently found in bioactive natural products and pharmaceuticals, e.g., indoprofen (anti-inflammatory),[1] lactonamycin (antibacterial),[2] and hericenone B (platelet aggregation inhibitory)[3] (Figure 1).

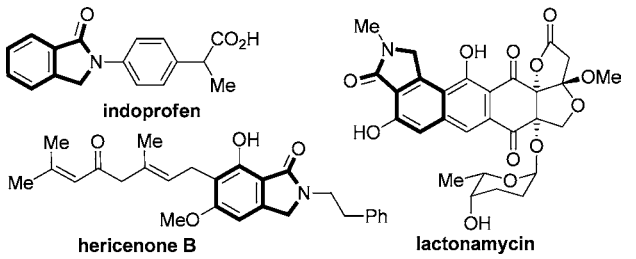
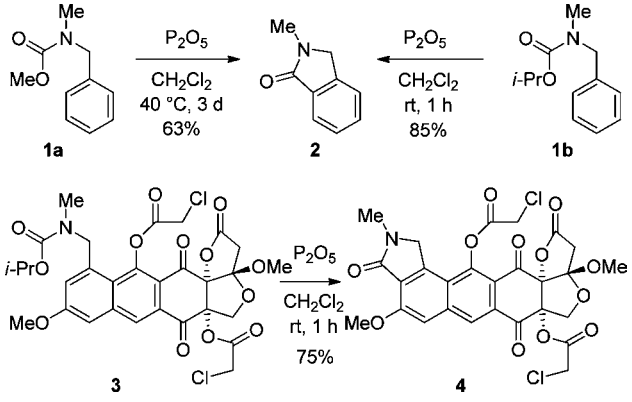


Figure 1. Natural and synthetic isoindolinones.

A variety of synthetic methods for simple and stable isoindolinones[4] have been employed: lactamization of *o*-(aminomethyl)benzoic acids, lithiation/cyclization of *o*-halobenzylcarbamates, metal-catalyzed cyclization via CO insertion of *o*-halobenzylamines, and monoreduction of phthalimides. However, for the synthesis of structurally complex isoindolinones, an ingenious strategy is needed due to the intractable properties of the isoindolinone skeleton. Staurosporines and lactonamycins, bioactive natural isoindolinones, are compounds that have challenged synthetic chemists due to air oxidation of the isoindolinones to the phthalimides and solubility issues.[5] Several direct cyclizations of isocyanates[6] and benzylamine derivatives, such as carbamoylxanthates[7] and nitrophenylureas,[8] as well as in situ metalation/carbonylation/lactamization,[9] have the potential to simplify the synthesis of complex molecules, though these reactions require strong acids and/or heating. As a representative example of simple direct cyclization, we have recently found that treatment of methyl carbamate **1a** with P_2O_5 in CH_2Cl_2 at 40 °C for 3 d provided isoindolinone **2** via a Bischler−Napieralski-type cyclization (Scheme 1).[10] Additionally, the corresponding isopropyl carbamate **1b** was much more smoothly converted into **2** even at room temperature for 1 h. This cyclization was successfully applied to the highly complex

Scheme 1. Discovery of Mild Conditions for the Isoindolinone Construction using Isopropyl Carbamates



molecule **3**, giving the desired isoindolinone **4**, a synthetic precursor of lactonamycins. The late-stage construction of the isoindolinone moiety of lactonamycins demonstrated utility of the isopropoxycarbonyl group, which is the best trigger for this cyclization as well as a convenient amino protecting group tolerant to various reaction conditions.[10]

The Bischler−Napieralski cyclization was originally reported in 1893 as a method for synthesizing 3,4-dihydroisoquinolines from *N*-acetylphenethylamines in the presence of P_2O_5.[11] Three years later, Pictet and Hubert applied this reaction to the synthesis of phenanthridinone from 2-ethoxycarbonylaminobiphenyl using zinc chloride.[12] The method was soon applied to other 3,4-dihydroisoquinolinones synthesized from *N*-alkoxycarbonylphenethylamines with various dehydrating agents,[13] along with the original 3,4-dihydroisoquinoline synthesis from *N*-acylphenethylamines.[14] Mechanistic studies of this series of cyclizations mainly focused on the *N*-acyl type;[15] cyclization reaction of *N*-acylphenethylamines using PCl_5 or $POCl_3$ involves the nitrilium ion, whereas *N*-acyl-*N*-alkylphenethyl-

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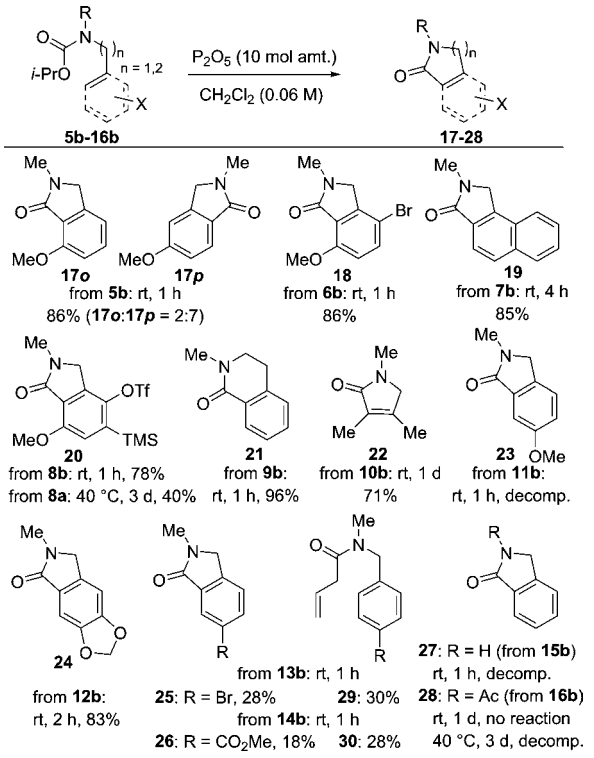
amines are said to cyclize via imidoyl chlorides or related species. These mechanisms are also believed to be applicable in the case of the *N*-alkoxycarbonyl type.[13f] The mechanism involving an imidoyl chloride, the most promising intermediate of the *N*-alkoxycarbonyl type cyclization, explains why isoindolinone synthesis with this kind of approach has not been examined closely. In the five-membered ring formation, one can expect that the corresponding intermediate is constrained by a disfavored angle that prevents attack by the aromatic ring.[16] Our recent success[10] suggests the possibility of a new mechanism to explain the smooth γ-lactam formation from the isopropyl carbamates. Herein, we demonstrate the utility of this reaction to synthesize a variety of lactams and discuss the mechanistic interpretation.

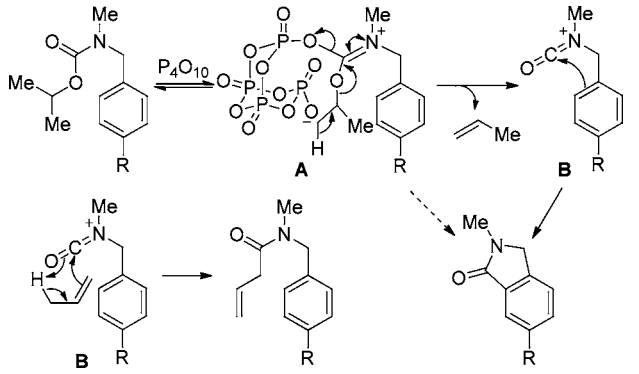
First, various isopropyl carbamates were subjected to the Bischler–Napieralski-type cyclization. The results of each isopropyl carbamate under our optimized conditions are summarized in Scheme 2.[17]

Scheme 2. Bischler–Napieralski-Type Cyclizations from Various Isopropyl Carbamates



Cyclization of various isopropyl carbamates (**5b**–**8b**) having the *ortho*- and/or *meta*-substituted benzyl groups proceeded smoothly to afford **17**–**20**. in particular, the multisubstituted carbamate **8b** was relatively sensitive, and cyclization of the corresponding methyl carbamate **8a** resulted in low yield of **20** concomitant with decomposition. Isoquinolinone **21** and the aliphatic lactam **22** were also obtained in good yield from **9b** and **10b**. On the other hand, *para*-substituted substrates were occasionally fractious (compounds **23**–**26**). *p*-Methoxybenzyl-carbamate **11b** was readily decomposed presumably due to the formation of the unstable *p*-quinone methide intermediate, whereas benzodioxole **12b** smoothly provided the corresponding isoindolinone **24**. In contrast, in the case of the electron-withdrawing *para*-substituents (**13b** and **14b**), the yields of **25** and **26** were poor and significant amounts of side products **29** and **30** were obtained. *N*-H-Carbamate **15b** and *N*-acetylcarbamate **16b** were not suitable for this cyclization to give no isoindolinones **27** and **28**. These results, especially unexpected formation of the side products **29** and **30**, suggested a new reasonable reaction mechanism (Scheme 3).

Scheme 3. Plausible Mechanism for Bischler–Napieralski-Type Cyclization



First, P_2O_5 (actual formula is P_4O_{10}) bonds to the carbonyl of the carbamate on the basis of the common mechanism for general Friedel–Clafts-type cyclizations to give intermediate **A**, an imidoyl phosphate. The imidoyl phosphate derived from phenethylcarbamate would be appropriate for dihydroisoquinolinone formation, but intermediate **A** is unfit for isoindolinone formation. Hydrogen abstraction from the isopropyl group causes elimination of propene to give a new intermediate, carbamoyl cation **B**, which allows smooth cyclization to give the γ-lactam. Electron-withdrawing groups (R = Br and CO_2Me), however, retard the cyclization. Instead, liberated propene can attack the carbonyl center via a carbonyl–ene reaction, giving alkene adducts such as **29** and **30**. Similar observation that treatment of the Boc-protected homobenzylamine with Tf_2O afforded a neutral isocyanate intermediate through release of isobutene would support this unprecedented carbamoyl cation formation.[18]

To assess the credibility of the proposed mechanism, various alkoxy groups in the carbamates were investigated under two different reaction conditions: method A, 1,2-dichloroethane, 84 °C, 1 d; and method B, dichloromethane, room temperature, 1 h (Table 1). Methyl carbamate **1a** was converted to isoindolinone **2** in 57% yield along with recovery of **1a** (31%) in method A, whereas almost no reaction occurred in method B (entries 1 and 3). Cyclization of isopropyl carbamate **1b** afforded **2** in high yield with both methods A and B (entries 4 and 6). *n*-Propyl carbamate **1c** and isobutyl carbamate **1d** yielded similar results as **1b** in method A (entries 8 and 11). Compounds **1b**–**d** are able to eliminate propene or isobutene via an imidoyl phosphate corresponding to intermediate **A**, producing intermediate **B**. The results of method B on **1b**–**d** indicate that ease of formation of intermediate **B** influences the cyclization rate (entries 6, 10, and 12). On the other hand, *tert*-butyl carbamate **1e**, expected as a rapid carbamoyl cation generator, was not suitable for this cyclization due to partial decomposition of **1e** (entries 13 and 14).[19] For comparison, treatment of **1e** with Tf_2O and DMAP[18a] resulted in decomposition whereas the same reaction using isopropyl carbamate **1b** afforded the desired isoindolinone in only 27%

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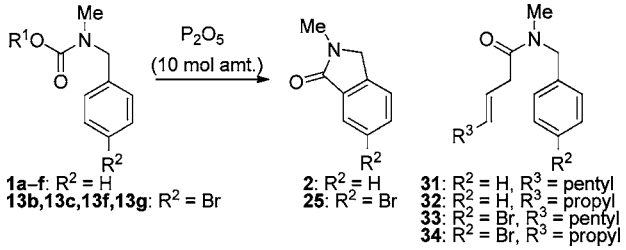
Table 1. Bischler–Napieralski-Type Cyclization of Various Carbamates and Competition Experiments with 1-Octene and 1-Hexene



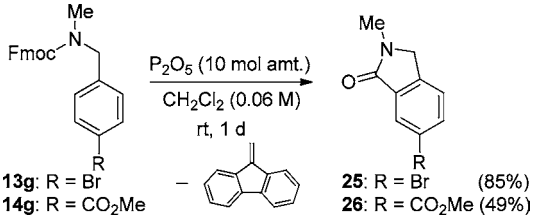
entry	substrate	R^1	method[a]	additive[b]	results (yield, %)
1	**1a**	methyl	A		**2** (57), **1a** (31)
2			A	1-octene	**2** (57), **1a** (35), **31** (2)
3			B		**2** (3), **1a** (85)
4	**1b**	isopropyl	A		**2** (86)
5			A	1-octene	**2**(75), **31** (1)
6			B		**2** (85)
7			B	1-hexene	**2** (61), **32** (14)
8	**1c**	*n*-propyl	A		**2** (86)
9			A	1-octene	**2** (76), **31** (1)
10			B		**2** (58), **1c** (22)
11	**1d**	isobutyl	A		**2** (85)
12			B		**2** (58), **1d** (25)
13	**1e**	*t*-butyl	A		**2** (30)
14			B		**2** (63)
15	**1f**	phenyl	A		**2** (51), **1f** (30)
16			A	1-octene	**2** (46), **1f** (44), **31** (0)
17	**13b**	isopropyl	B		**25** (28), **29** (30)
18			B	1-hexene	**25** (4), **34** (30)
19	**13c**	*n*-propyl	B[c]		**25** (41), **29** (30)
20	**13f**	phenyl	A		**25** (49), **13f** (34)
21			A	1-octene	**25** (11), **13f** (59), **33** (0)

[a]Method A: carbamate and P_2O_5 in 1,2-dichloroethane (0.06 M), 84 °C, 1 d. Method B: carbamate and P_2O_5 in dichloromethane (0.06 M), rt, 1 h. [b]Alkene (10 mol amounts) was added to the carbamate solution prior to addition of P_2O_5. [c]Reaction time: 1 d.

yield along with detectable amounts of *N*-methylbenzylamine and its *N*-triflate.[20] Tf_2O reversibly binds to either oxygen or nitrogen of the carbamate,[21] providing the carbamoyl cation and the *N*-sulfonyl carbamate, respectively. Each intermediate can be attacked by DMAP to give the above side products. Highly oxophilic P_2O_5 would selectively bind to oxygen to provide intermediate **B** via the imidoyl phosphate. Phenyl carbamate **1f**, without an alkyl group to eliminate, produced isoindolinone **2** with method A (entry 15), suggesting direct cyclization from imidoyl phosphate without passing intermediate **B** at higher temperature.

Similar to the case of **13b** (Table 1 entry 17 and Scheme 2), cyclization of **13c** using method B afforded **25** (41%) and **29** (30%) (entry 19). In addition, the presence of excess amounts of 1-hexene in the **13b** reaction mixture caused competitive addition of 1-hexene over propene, giving **34** in 30% yield (entry 18). This competitive experiment was applied to other substrates. Formation of the externally attacked **31** or **32** was observed in the case of **1a–c** (entries 2, 5, 7, and 9), whereas phenyl carbamates **1f** and **13f** provided no carbonyl–ene adducts (entries 16 and 21), despite their sufficient reactivity in method A (entries 15 and 20). Formation of carbonyl–ene adducts implied formation of intermediate **B**, which has an extremely electrophilic center.[22] These results clearly indicate that the formation of intermediate **B** is a key step for this γ-lactam formation under such mild conditions. Thus, we reached to other useful carbamates containing an alkoxy group with an acidic β-hydrogen and without a γ-hydrogen, for the effective construction of isoindolinones with electron-poor aromatic groups. The 9-fluorenylmethyl, phenethyl, and homoallyl groups satisfied these requirements, and we selected the Fmoc-protected benzylmethylamines (9-fluorenylmethyl carbamate of benzylmethylamine) due to their easy preparation and reactivity in cyclization.[17] Thus, Fmoc-amine **13g**, which releases dibenzofulvene by treatment of P_2O_5, was transformed into isoindolinone **25** in 85% yield without any side products (Scheme 4). Furthermore, (*p*-methoxycarbonyl)-benzylcarbamate **14g** provided isoindolinone **26** in better yield than the **14b** case (Scheme 2).

Scheme 4. Improved Cyclization Using Fmoc-Protected Benzylmethylamines



In summary, we discovered a simple and efficient method for construction of isoindolinones with a new reaction mechanism. Most isoindolinones could be synthesized by treatment of isopropyl carbamates of benzylamines with P_2O_5 under the mild conditions. Furthermore, consideration of the mechanism led to the use of Fmoc-benzylamines as a complement to the construction of isoindolinones with electron-deficient aryl groups. The simple and versatile method described here would be applicable to divergent syntheses demanded by recent pharmaceutical developments and to natural product syntheses, as exemplified by our previous success of the total syntheses of lactonamycins.[10]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) Formation of the carbonyl−ene adduct at entry 2 in Table 1 could be regarded as a partial contribution of intermediate **B** generated via an intramolecular S_N2 substitution by the phosphate residue at the methyl center of the imidoyl phosphate.