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N-Capping of Primary Amines with 2-Acylbenzaldehydes To Give Isoindolinones

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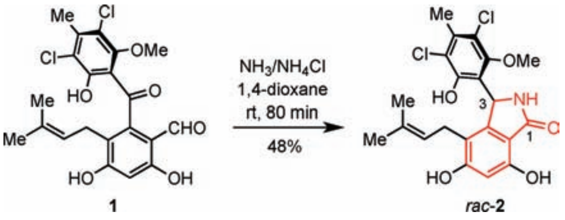
ABSTRACT

A unique reactivity pattern, first observed in the conversion of the marine natural product pestalone into pestalachloride A, was investigated. It was shown that 2-formyl-arylketones smoothly react with ammonia and primary amines, respectively, under mild conditions to afford 3-substituted isoindolinones in high yield. The reaction represents a new option for the derivatization (*N*-capping) of primary amines. As the substrates are readily accessible the methodology opens a short and modular access to pharmaceutically relevant substituted isoindolinones.

The natural product pestalone (**1**), isolated by W. Fenical and co-workers in 2001 from a cofermentation of a marine fungus and a marine bacterium, was reported to possess a strong antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MIC = 37 ng/mL).[1] A few years later, the structurally somewhat related compound pestalachloride A (*rac*-**2**) was discovered as a metabolite produced by the endophytic plant fungus *Pestalotiopsis adusta* and shown to exhibit antifungal activities against different plant pathogenic fungi.[2] Recently, we have accomplished an efficient total synthesis of **1** which enabled us to also study its reactivity and to identify some rather unexpected transformations of the *ortho*-formyl-benzophenone substructure.[3] In particular, we could show that **1** can be converted into the isoindolinone *rac*-**2** in a single step by simply treating a dioxane solution of **1** with NH_3 in aqueous NH_4Cl (pH = 8.0) at room temperature (Scheme 1).

Scheme 1. One-Step Conversion of Pestalone (**1**) into Pestalachloride A (**2**)



Noteworthy, the isoindolinone (phthalimidine) motif occurs as a core structure not only in several other natural products such as stachybotrin C[4] and lennoxamine[5] but also in a number of pharmacologically relevant synthetic molecules, such as pagoclone[6] or (*S*)-PD 172938[7] (Figure 1). The biological potential of the isoindolinone class of

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(1) Cueto, M.; Jensen, P. R.; Kauffman, C.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Nat. Prod.* **2001**, *64*, 1444–1446.

(2) Li, E.; Jiang, L.; Guo, L.; Zhang, H.; Che, Y. *Bioorg. Med. Chem.* **2008**, *16*, 7894–7899.

(3) Slavov, N.; Cvengros, J.; Neudörfl, J.-M.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2010**, *49*, 7588–7591.

(4) (a) Nozawa, Y.; Yamamoto, K.; Ito, M.; Sakai, N.; Mizoue, K.; Mizobe, F.; Hanada, K. *J. Antibiot.* **1997**, *50*, 635–640. (b) Nozawa, Y.; Ito, M.; Sugawara, K.; Hanada, K.; Mizoue, K. *J. Antibiot.* **1997**, *50*, 641–645.

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(9) Shirasaka, T.; Kunitake, T.; Tsuneyoshi, I. *Brain Res.* **2009**, *1300*, 105–113.

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10.1021/ol202271k

compounds in general is reflected, for instance, by antidopaminergic,[7] anxiolytic,[8] hypnotic,[9] antimicrobial,[10] antiviral,[11] and antitumoral[12] activities.

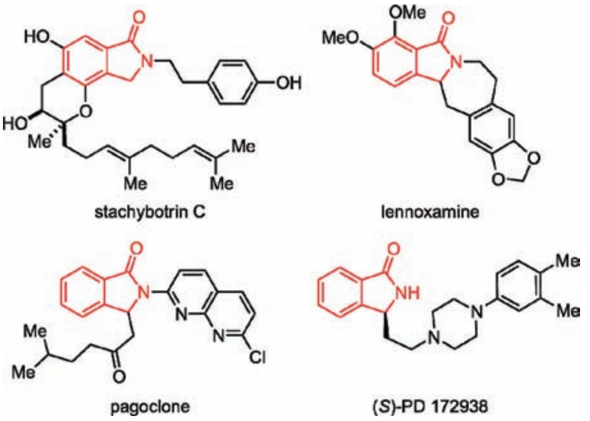


Figure 1. Natural products and biologically active compounds containing the isoindolin-1-one moiety.

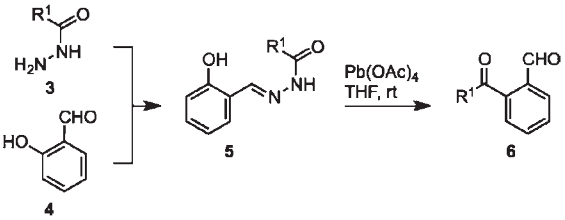
While early methods for the synthesis of isoindolinones are based on condensation reactions[13] the growing importance of this compound class is reflected by the recent development of novel approaches exploiting, for instance, radical cyclization,[14] *ortho*-lithiation/cyclization,[15] Pd-catalyzed cyclo-carbonylation,[16] In-mediated allylation/cyclization of *N*-sulfinyl imines,[17] Pd-catalyzed α-substitution of isoindolinones,[18] Rh-catalyzed arylation of 2-formylbenzoate-derived *N*-tosylimines,[19] and Ni(0) mediated cyclization of *N*-benzoylaminals.[20]

Nevertheless, most of the existing methods suffer from certain limitations with respect to yield, substrate scope, or apparative requirements. Most noticeable, they are not particularly well suited for the preparation of compound libraries. Therefore, the search for an operational convenient, modular, and broadly applicable isoindolinone synthesis still represents a challenging research task.

Inspired by the surprisingly facile formation of the isoindolinone **2** from the highly functionalized *ortho*-formylbenzophenone **1** we decided to probe this novel type of lactamization reaction as a general new entry to isoindolinones also using less complex substrates.

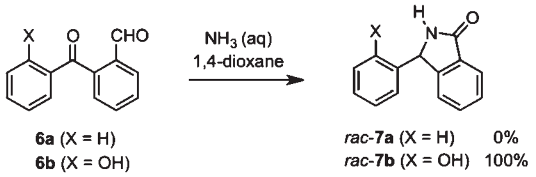
To prepare a variety of different 2-acylbenzaldehydes of type **6** we employed the protocol developed by Kotali et al.[21] which proved to be highly reliable. For this purpose, a series of *N*-acylhydrazines (**3**) were condensed with salicylic aldehyde (**4**) to form *N*-aroylhydrazones **5**, which were then oxidized with lead tetraacetate to give the desired substrates (**6**) in typically 45–70% overall yield (Scheme 2).

Scheme 2. Preparation of 2-Acylbenzaldehydes According to Kotali



We started our study with *ortho*-formylbenzophenone (**6a**) as a model substrate which can be considered as a most simple pestalone analog. Initial attempts to convert **6a** into the corresponding isoindolinone *rac*-**7a** under the conditions used before for the conversion of **1** into *rac*-**2**, i.e. by treating a 1,4-dioxane solution of **6a** with aqueous NH_3/NH_4Cl solution (pH = 8.0) at room temperature,[3] resulted only in the formation of undefined, highly polar (possibly oligomeric) products. Treatment of **6a** with unbuffered aqueous NH_3 (4 equiv) was also not successful (Scheme 3).

Scheme 3. Treatment of **6a** and **6b** with Ammonia



Interestingly, 2-(2-hydroxybenzoyl)benzaldehyde (**6b**), which more closely resembles the core functionality of

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(11) (a) Maugeri, C.; Alisi, M. A.; Apicella, C.; Cellai, L.; Dragone, P.; Fioravanzo, E.; Florio, S.; Furlotti, G.; Mangano, G.; Ombrato, R.; Luisi, R.; Pompei, R.; Rincicotti, V.; Russo, V.; Vitiello, M.; Cazzolla, N. *Bioorg. Med. Chem.* **2008**, *16*, 3091–3107. (b) Zhao, X. Z.; Maddali, K.; Marchand, C.; Pommier, Y.; Burke, T. R. *Bioorg. Med. Chem.* **2009**, *17*, 5318–5324.

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(14) López-Valdez, G.; Olguín-Uribe, S.; Millan-Ortíz, A.; Gamez-Montaño, R.; Miranda, L. D. *Tetrahedron* **2011**, *67*, 2693–2701.

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(19) (a) Wang, Z.; Feng, C.; Xu, M.; Lin, G. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (b) Kurihara, K.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2009**, *351*, 260–270.

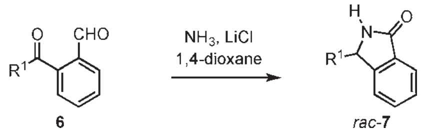
(20) Shacklady-McAtee, D. M.; Dasgupta, S.; Watson, M. P. *Org. Lett.* **2011**, *13*, 3490–3493.

(21) (a) Kotali, A.; Papapetrou, M.; Dimos, V.; Harris, P. *Org. Prep. Proced. Int.* **1998**, *30*, 177–181. (b) Kotali, A.; Tsoungas, P. G. *Tetrahedron Lett.* **1987**, *28*, 4321–4322.

pestalone, afforded the desired 3-phenylisoindolinone *rac*-**7b** in quantitative yield on reaction with aqueous NH_3 in 1,4-dioxane at room temperature (Scheme 3).

While the (acidic) phenolic OH group obviously exerts a beneficial effect on the reaction course we felt challenged to find conditions for the transformation of "non-activated" substrates such as **6a**. To mimic the assisting effect of the phenol OH, we performed the reaction of **6a** (with excess NH_3 in 1,4-dioxane at room temperature) in the presence of LiCl (1 equiv). We were pleased to find that the expected product, i.e. 3-phenylisoindolinone (*rac*-**7a**), was indeed obtained under these conditions in 74% yield. As Table 1 shows, this procedure could also be successfully applied to the conversion of two other *ortho*-formylbenzophenones to give the corresponding *N*-unsubstituted isoindolinones (*rac*-**7b** and *rac*-**7d**) in moderate yield. However, the electron-poor substrates (**6c** and **6e**) and the alkanoyl-substituted benzaldehyde **6f** did not afford any of the desired products. Instead red and highly polar "polymers" were formed in these cases (also at lower temperatures).

Table 1. Formation of Isoindolinones[a]



entry	substrate	R^1	product	yield[b]
1	**6a**	C_6H_5	*rac*-**7a**	74%
2	**6b**	*o*-OHC_6H_4	*rac*-**7b**	63%
3	**6c**	*p*-$NO_2C_6H_4$	*rac*-**7c**	0%
4	**6d**	*p*-$OMeC_6H_4$	*rac*-**7d**	50%
5	**6e**	pyridin-4-yl	*rac*-**7e**	0%
6	**6f**	C_2H_5	*rac*-**7f**	0%

[a] Conditions: NH_3 (10% in H_2O), 1,4-dioxane, LiCl (1 equiv), 5 h rt. [b] Isolated yield.

At this point, we contemplated the mechanism of the isoindolinone formation.[3,22] As shown in Scheme 4 we assume an initial (possibly reversible) formation of a cyclic bis-hemiaminal (**9**), from which a hydroxyisoindole (**11**) is generated by water elimination, probably via a cationic intermediate of type **10**. Finally, tautomerization of **11** leads to the thermodynamically more stable lactame *rac*-**7**/**8**.

Next, we investigated the possibility of also reacting primary amines (instead of ammonia) with 2-acylbenzaldehydes in order to obtain *N*-alkylated isoindolinones of type *rac*-**8**. Mechanistic considerations (Scheme 4) suggested that the presence of a weak acid should facilitate both the formation of an iminium cation (of type **10**) and the final tautomerization step.[13b] In an initial experiment we treated **6a** with an excess of aqueous methylamine in the presence of 1 equiv of acetic acid. While full conversion of **6a** was detected after 3.5 h the desired *N*-methyl-3-phenylisoindolin-1-one (*rac*-**8a**) was obtained in only 14% yield. However, the reaction could be greatly optimized by varying the ratio of methylamine and acetic acid. With only 2 equiv of the amine in the presense of 2.3 equiv of acetic acid the product *rac*-**8a** was formed in virtually quantitative yield within less than 1 min at room temperature (Table 2). The structure of *rac*-**8a** was confirmed by X-ray crystal structure analysis (Figure 2).

Scheme 4. Proposed Mechanistic Pathway

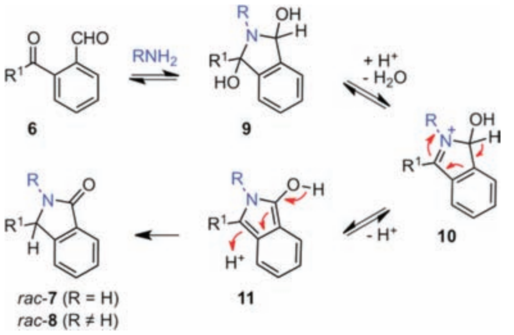
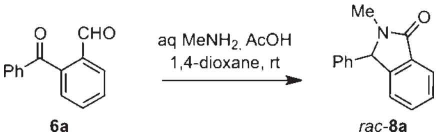


Table 2. Optimization of the Reaction Conditions



entry	aq. $MeNH_2$	acetic acid	time[a]	yield[b]
1	10.0 equiv	1.0 equiv	3.5 h	14%
2	5.0 equiv	0.4 equiv	5.0 h	19%
3	5.0 equiv	1.0 equiv	25 min	24%
4	5.0 equiv	2.0 equiv	25 min	36%
5	2.0 equiv	2.3 equiv	1 min	quant
6	1.1 equiv	1.1 equiv	1 min	77%

[a] Full conversion of starting material (TLC). [b] Isolated yield.

Using the reaction of **6a** with methylamine (Table 2, entry 5) as a standard, we briefly evaluated the effect of different solvents. While other etheral solvents such as THF, 2-methyl-THF, and diethylether proved to be much less effective as compared to 1,4-dioxane, a quantitative yield of *rac*-**8a** was also obtained in MeOH. However, the reaction was slower in this case requiring 5 min to reach full conversion (compared to 1 min in 1,4-dioxane). It also proved important to run the reactions under inert gas in order to suppress oxidative side reactions.

Having identified efficient and reliable conditions for the preparation of *rac*-**8a** we next probed the scope of the method employing a set of different *ortho*-acyl-benzaldehydes also using benzylamine as a second primary amine. The results, summarized in Table 3, show that

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[22] Wan, J.; Zhou, J.; Mao, H.; Pan, Y.; Wu, A. *Tetrahedron* **2008**, *64*, 11115–11123.

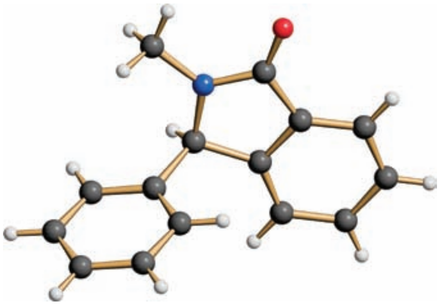
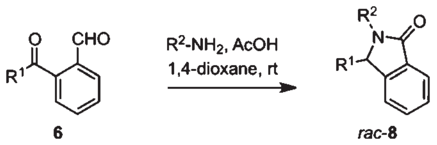


Figure 2. Structure of *rac*-**8a** in the crystalline state.

the expected lactames (2,3-disubstituted isoindolin-1-ones) were reliably formed in high yield without the neccessity of individual optimization. Only in the reaction of *ortho*-propanoyl-benzaldehyde with methylamine a lower yield (43%) was observed (entry 6).

Table 3. Synthesis of Various *N*-Alkylated Isoindolinones[a]

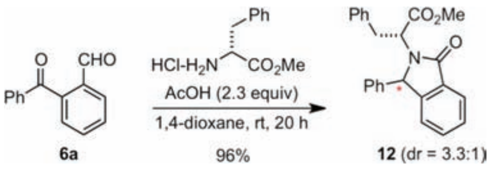


entry	R^1	R^2	product	yield[b]
1	C_6H_5	Me	*rac*-**8a**	>99%
2	*o*-OHC_6H_4	Me	*rac*-**8b**	93%
3	*p*-$NO_2C_6H_4$	Me	*rac*-**8c**	69%
4	*p*-$OMeC_6H_4$	Me	*rac*-**8d**	82%
5	pyridin-4-yl	Me	*rac*-**8e**	72%
6	C_2H_5	Me	*rac*-**8f**	43%
7	C_6H_5	benzyl	*rac*-**8g**	92%
8	*o*-OHC_6H_4	benzyl	*rac*-**8h**	77%
9	*p*-$NO_2C_6H_4$	benzyl	*rac*-**8i**	90%
10	*p*-$OMeC_6H_4$	benzyl	*rac*-**8j**	76%
11	pyridin-4-yl	benzyl	*rac*-**8k**	88%
12	C_2H_5	benzyl	*rac*-**8l**	71%

[a] Conditions: $MeNH_2$ in H_2O (2.0 equiv), AcOH (2.3 equiv), 1,4-dioxane, 20 °C, Ar atmosphere. [b] Isolated yield.

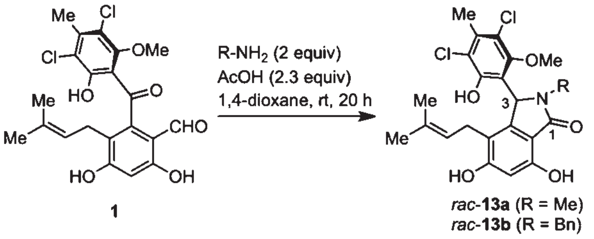
In an additional experiment, a chiral amine, i.e. D-phenylalanine methyl ester hydrochloride, was reacted with **6a** to smoothly afford the isoindolinone derivative **12** in 96% yield with a significant degree of asymmetric induction (dr = 3.3:1) (Scheme 5).[23]

Scheme 5. Diastereoselective Isoindolinone Formation by *N*-Capping of a Chiral Amine



Finally, we probed the ability of the natural *ortho*-formylbenzophenone pestalone (**1**) itself to act as an *N*-capping agent for primary amines. And indeed, treatment of **1** with either methyl amine or benzyl amine under the established conditions resulted in the formation of the corresponding isoindolinones *rac*-**13a** (65%) or *rac*-**13b** (99%), respectively (Scheme 6).

Scheme 6. *N*-Capping of Primary Amines by Pestalone (**1**) To Give *N*-Alkylated Pestalachloride A Derivatives



In conclusion, we have shown that certain 2-acylbenzaldehydes efficiently react with ammonia or primary amines under mild conditions to give substituted isoindolinones. Due to the modularity, operational simplicity, and reliability it is likely that the method will find future exploitation in the synthesis of compound libraries in the context of pharmaceutical research.

The results also suggest that the natural product pestalone (**1**) can be considered as a reactive agent able to capture primary amines (*N*-capping) as *N*-substituted derivatives of pestalachloride A. Thus, the discovered reactivity pattern may even be relevant for the mechanistic understanding of the antibiotic activity of **1** in the future. Current studies in this laboratory focus on mechanistic and stereochemical aspects of this new method of isoindolone synthesis.

Acknowledgment. D.C.G. thanks the Alexander von Humboldt Foundation for a postdoctoral fellowship.

Supporting Information Available. Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. X-ray crystallographic data for **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] The two diastereomers, clearly apperaring as two distinct sets of signals in the ^{13}C NMR, were not separated.