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Design and synthesis of α-aminonitrile-functionalized novel retinoids

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ABSTRACT

We have developed an expedient one-pot method for the synthesis of α-aminonitrile-functionalized new retinoids via a three-component condensation of β-cyclocitral, amine, and TMSCN (trimethyl silylcyanide) in the presence of a catalytic amount of indium(III) chloride in water. The reactions proceeded smoothly at room temperature in water to generate the corresponding retinoids in moderate to excellent yields (85–92%). In addition, the utility of this reaction was demonstrated to synthesize boron-containing retinoids.

All trans retinoic acid (ATRA) and its metabolites play a crucial role in adult physiological functions such as promoting growth and differentiation, regulating apoptosis, and maintaining homeostasis in numerous tissues and also play a crucial role in a variety of processes such as patterning of anterior–posterior axis and development of heart, brain, and limbs.[1,2] ATRA is being used in differentiation therapy of cancer, in cancer chemoprevention, and for the treatment of dermatological diseases, including acne, psoriasis, and ichthyosis.[3] Recently, ATRA has proven useful in cancer chemotherapy.[4a] One of the most impressive effects of ATRA is on acute promyelocytic leukaemia (APL).[4b] The success of RA treatment is limited due to its rapid degradation in the body that leads to non-specific toxicity and retinoic acid syndrome. So the discovery of retinoids with resistance to metabolism and/or restricted activity on different receptors is an active area of research. For our ongoing chemical biology project, we have long-term goal to develop new antagonist and agonist compounds in order to target specific pathways to identify new gene targets of these pathways. Toward this goal, we focused on retinoic signaling pathway, as it plays key roles in patterning the body axis and in the formation of many organs and defects in this signaling pathway cause many diseases.[5] In this Letter, we report the synthesis of α-aminonitrile-containing novel retinoids and used this procedure to synthesize boron-containing α-aminonitrile-functionalized retinoids. Boron-containing retinoids are completely new class of retinoids, and may open new avenue to study retinoic acid signaling biology. The use of boron atoms in pharmaceutical drug design possesses a high potential for discovery of new biological activity.[6–10] Among various boron compounds synthesized, much attention has been paid to boronic acid-containing peptides such as Velcade and DPP-IV inhibitors.[8] In these boropeptides, a carboxylic acid has been replaced by a boronic acid group.

As α-aminonitrile functionalities are significantly important intermediates[11] for the synthesis of a wide variety of amino acids, amides, diamines, and nitrogen-containing heterocycles, we hypothesized that introduction of α-aminonitrile moieties to synthesize novel retinoid libraries may increase the efficacy and potency in ATRA therapy and also help to study the RA signaling biology to identify new biomarkers in this pathway. For this reason, we planned to synthesize compounds **2**–**4** as new retinoic acid analogues by introducing a phenyl ring in place of alkene spacers (Fig. 1) and also the alkene functionalized as imine and its α-aminonitrile derivatives by keeping hydrophobic part (cycloalkene) and carboxylic acid intact.

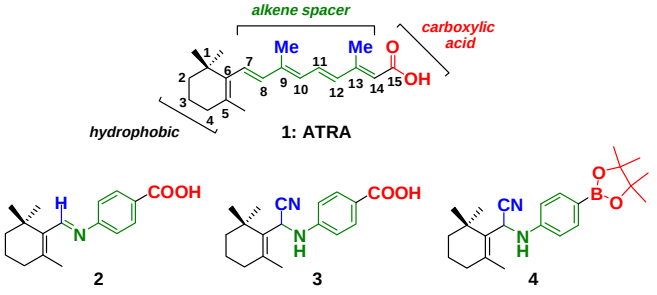

Figure 1. Structure of ATRA and new retinoids.

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To synthesize new retinoids **3** and **4** and further functionalize into new derivatives, we chose the cyanation of the imine scaffold **2** (Fig. 1) as the key step to synthesize the α-aminonitrile-functionalized constrained new retinoids. The latter substrates bear an α-aminonitrile moiety, which to the best of our knowledge has not been reported previously in this system. More recently, indium(III) compounds have been demonstrated to be mild, efficient, and water-tolerant Lewis acids for various organic transformations.[12] In contrast to classical Lewis acids, which often are required in stoichiometric quantities, indium(III) compounds readily promote a wide variety of organic reactions in catalytic quantities soluble both in organic solvents and in aqueous media. We chose indium(III) chloride ($InCl_3$) as the Lewis acid catalyst for the synthesis of α-aminonitrile-functionalized new retinoids.

In our preliminary experiments, we investigated the optimization of reaction conditions regarding both the catalyst and solvent. We concentrated only β-cyclocitral **5** because this is the most important part in ATRA as hydrophobic part as shown in Figure 1 and our objective was to keep this part intact and introduce α-aminonitrile and phenyl ring system as polyene chain spacer in ATRA.

For this purpose, β-cyclocitral **5** and methyl-4-amino benzoate **6a** were chosen as model substrates for the synthesis of representative compound **3a** (Scheme 1).

The reaction took place efficiently at room temperature in water and furnished the desired product **3a** in 86% yield (Scheme 1) as a white solid. The product was filtered and washed with water and hexane to isolate it in an analytically pure form without column chromatography. ^1H, ^{13}C, and HRMS corroborate the formation of the α-aminonitrile-functionalized retinoid **3a**.[13]

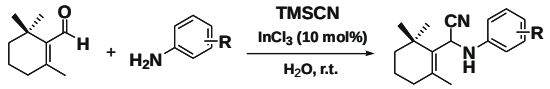
Although the use of an $InCl_3$ as a catalyst permits facile recycle with the aqueous phase. To demonstrate catalyst recovery without loss of activity, we performed an experiment to reuse the catalyst after the filtration of the product **3a**. We used the same aqueous phase for second set of reactions but the activity was reduced and the reaction was not complete even after stirring the reaction mixture at room temperature for 48 h and the isolated yield of **3a** was 52%.

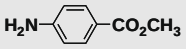
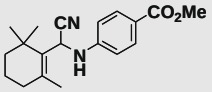
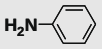
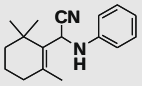
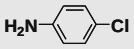
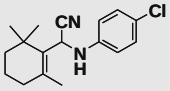
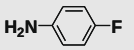
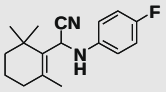
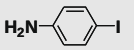
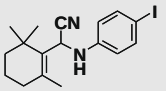
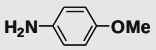
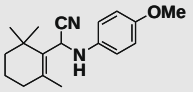
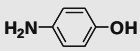
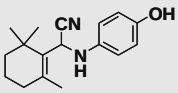
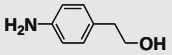
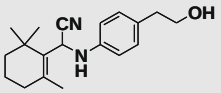
Encouraged by above results, we continued our task of exploring the reactivity of different amines (Table 1, entries **6b**–**h**) with β-cyclocitral **5** and TMSCN under similar reaction conditions. Table 1 shows a number of examples of this chemistry. As shown in Table 1, all amines could efficiently undergo reactions with β-cyclocitral **5** and TMSCN to give the products in good to excellent yields (Table 1, entries 2–8). We have chosen variety of amines bearing electron-donating and electron-withdrawing groups to synthesize new retinoids. The amine substrates, such as *p*-iodo (**3e**: 93%, Table 1, entry 5), *p*-methoxy (**3f**: 90%, Table 1, entry 6), and 2-(4-aminophenyl)-ethanol (**3h**: 92%, Table 1, entry 8) were obtained in higher yields, and overall the process was convenient for synthesizing library of new class of retinoids. The experimental procedure is very simple and generally involves mixing and stirring the three components together at ambient temperature in presence of catalytic amount of $InCl_3$ for 4–6 h.

A typical solvent is water although water/methanol mixture can also be used. It is noteworthy that the reaction does not require anhydrous or oxygen-free conditions and is also readily adaptable to synthesis for the construction of combinatorial libraries to scale-up. All the products were isolated as air-stable white solids.

Scheme 1. Synthesis of α-aminonitrile-functionalized retinoids.

Table 1
Synthesis of α-aminonitrile-functionalized retinoic acid analogues **3** by the reaction of β-cyclocitral **5** with amines **6** and TMSCN in presence of catalytic amount of $InCl_3$[a]

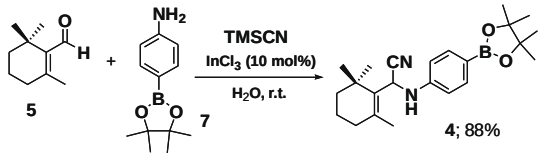


Entry	Amine (**6a**–**h**)	Product (**3a**–**h**)	Yield[b] (%)
1			86
2			82
3			80
4			78
5			93
6			90
7			85
8			92

[a] All reactions were performed using 1 equiv of aldehyde and 1 equiv of amine and 1.2 equiv of TMSCN in water 4–6 h.
[b] Isolated yield refers to aldehyde.

After generalizing the procedure, we turned our attention toward the synthesis of boron-containing α-aminonitrile-functionalized retinoid **4**. In this case, β-cyclocitral **5** was treated with 4-aminophenylboronic acid pinacol ester **7** in the presence of catalytic amount of $InCl_3$ and TMSCN and the desired boron-containing retinoid **4** was isolated in 88% yield (Scheme 2). From literature search, we found this to be the first example where α-aminonitrile-functionalized boron-containing retinoids were synthesized.

In summary, we have developed an expedient one-pot method for the synthesis of new class of constrained retinoids (β-cyclocitral-derived α-aminonitriles) via a three-component condensation of β-cyclocitral, amine, and TMSCN in the presence of a catalytic amount of indium(III) chloride in water. This method is quite general and it works well with a wide variety of amines at room temperature. This method is simple and attractive for synthesizing highly important small molecular retinoid libraries. This is the first example where we synthesized boron- and α-aminonitrile-con-



Scheme 2. Synthesis of boron-containing retinoid **4**.

taining retinoids. In future this will open a new avenue, in retinoic acid signaling pathways to identify new biomarkers, which may be used as therapeutic agents for diseases induced by RA pathways. Experiments are currently underway to test the biological activity of these derivatives and to determine their utility as modulators of retinoic acid signaling pathways.

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Supplementary data

Supplementary data (Experimental procedures and copies of ^{1}H, ^{13}C NMR) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.119.

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13. *General procedure for the synthesis of retinoids* (Table 1): Into a 10-mL round-bottomed flask were added β-cyclocitral (1.0 mmol), amine (1.0 mmol), TMSCN (1.2 mmol), H_2O (2 mL), and $InCl_3$ (0.1 mmol) sequentially. The reaction mixture was stirred vigorously at room temperature and the progress of the reaction was monitored by TLC. After stirring for 4–6 h at room temperature the solid that was obtained was filtered and washed with water and hexane to yield the desired product retinoids (**4a**–**h** and **7**).
Compound **3a**: R_f = 0.61 (ethyl acetate/hexane = 1:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 3H), 1.16 (s, 3H), 1.45–1.70 (m, 4H), 2.03 (s, 3H), 2.07–2.09 (m, 2H), 3.89 (s, 3H), 4.08–4.09 (d, J = 3 Hz, 1H), 4.71–4.73 (d, J = 6 Hz, 1H), 6.72–6.75 (d, J = 9 Hz, 2H), 7.96–7.99 (d, J = 9 Hz, 2H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 168.0, 149.8, 139.3, 134.8, 132.1, 122.2, 119.0, 112.6, 52.3, 43.8, 39.0, 35.7, 34.4, 28.8, 27.6, 21.9, 19.3 ppm; HRMS (EI, *m/z*): $[M+H]^+$, calcd for $C_{19}H_{25}N_2O_2$: 313.1916, found: 313.1922.
Compound **4**: R_f = 0.65 (ethyl acetate/hexane = 1:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.15 (s, 3H), 1.35 (s, 12H), 1.40–1.70 (m, 4H), 2.03 (s, 3H), 2.05–2.14 (m, 2H), 3.83–3.84 (d, J = 3 Hz, 1H), 4.70–4.72 (d, J = 6 Hz, 1H), 6.72–6.75 (d, J = 9 Hz, 2H), 7.73–7.76 (d, J = 9 Hz, 2H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 149.2, 137.0, 136.9, 133.8, 120.2, 112.7, 83.8, 44.5, 39.2, 36.4, 34.0, 28.5, 27.9, 25.3, 25.2, 21.8, 18.9 ppm; HRMS (EI, *m/z*): $[M+Na]^+$, calcd for $C_{23}H_{33}BN_2NaO_2$: 403.2533, found: 403.2543.