Hypervalent Iodine Oxidative Rearrangement of Anthranilamides, Salicylamides and Some β-Substituted Amides: A New and Convenient Synthesis of 2-Benzimidazolones, 2-Benzoxazolones and Related Compounds

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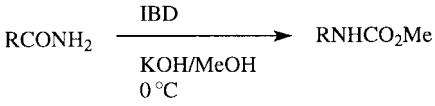
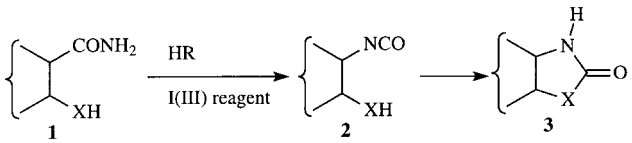
Abstract: Oxidation of anthranilamides, salicylamides and some β-substituted amides with iodobenzene diacetate in methanolic potassium hydroxide led to a new and convenient synthesis of 2-benzimidazolones, 2-benzoxazolones and related compounds, respectively. The reaction probably occurs via initial Hofmann-type rearrangement followed by intramolecular cyclization of intermediate isocyanate.

Key words: hypervalent iodine, 2-benzimidazolones, 2-benzoxazolones, Hofmann rearrangement, hetereocycles, cyclization

Hypervalent iodine reagents have gained wide acceptance in organic synthesis in recent years.[1–9] Organoiodine(III) reagents, namely, iodobenzene diacetate (IBD)[10] and [hydroxy(tosyloxy)iodo]benzene,[11] iodobenzene bistrifluoroacetate (IBTA)[12,13] and iodosobenzene-formic acid[14] have been employed effectively for the Hofmann-type rearrangement (HR) of carboxamides to the corresponding isocyanates which react rapidly with various nucleophiles, to form the corresponding products such as carbamates (Eq. 1)[10]. Adopting this process to heterocyclic synthesis,[8-10] we have developed a new and efficient synthesis of 2-benzimidazolones **5a–h**, 2-benzoxazolones **5i, 5j** and related compounds **7,9,11**.

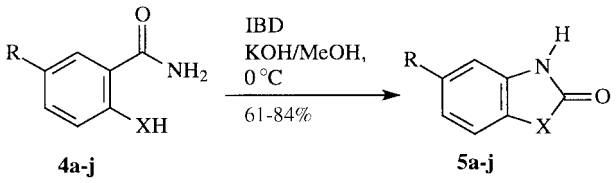


The synthetic strategy used in the present work is based on the idea that carboxamides **1** bearing nucleophilic substituents XH at their β-position (or *ortho* position) upon HR might generate in situ isocyanate **2**, which upon subsequent intramolecular nucleophilic attack by the XH group could afford the cyclized product of general formula **3** (Eq. 2)



1 **2** **3**

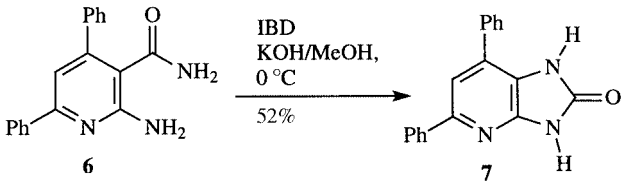
Accordingly, we first attempted the oxidation of the anthranilamide **4a** with IBD-KOH/MeOH[10] The reaction afforded the expected 2-benzimidazolone (**5a**, 82% yield) as a crystalline solid. The generality of this facile 2-benzimidazolone synthesis was established by treating other *N*-substituted anthranilamides **4b–h** with IBD under same conditions to give the corresponding benzimidazolones **5b–h** (Scheme 1) in 61–84% yields (Table).



4a-j **5a-j**

Scheme 1

Following the same approach, 2-amino-4,6-diphenyl-3-pyridinecarboxamide **(6)** was also converted to the 4,6-diphenyl-3-*H*-imidazolo[5,4-*b*]pyridin-2-one (**7**), a compound which is known to possess antibacterial activity (Scheme 2).[17]



6 **7**

Scheme 2

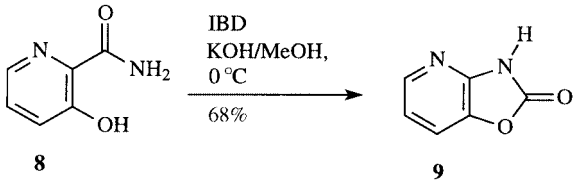
Based on these encouraging results, we carried out the oxidation of salicylamide **4i**, a case in which the intramolecular nucleophile is the phenolic hydroxyl group. This reaction indeed afforded the expected product, 2-benzoxazolone (**5i**) in 80% yield. This procedure was successful for the conversion of 5-chlorosalicylamide **(4j)** to 5-chloro-2-benzoxazolone (**5j**) (Scheme 1), which is reported to be useful as a skeletal muscle relaxant.[18] Further examples of such 2-oxazolones synthesis accomplished during this

Table Physical Data of 2-Benzimidazolones, 2-Benzoxazolones and Related Compounds

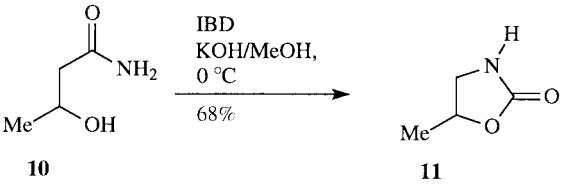
Product	R	X	Yield (%)[a]	Mp (°C) (Lit.) or bp (°C/Torr) (Lit.)[b]
5a	H	NH	82	307 (307–308)[15,16]
5b	Cl	NH	61	324–326 (324–326)[24,25]
5c	H	NMe	71	190–191 (190)[26]
5d	H	NEt	71	120–121 (122)[26,27]
5e	H	NPr	72	103–104 (102)[26,27]
5f	H	NPr-*i*	81	126–128 (128–129)[26,28]
5g	H	NBu	72	97–98 (98)[26,27]
5h	H	NBn	84	197–198 (196–198)[26,29]
5i	H	O	80	137–138 (137–139)[30]
5j	Cl	O	68	189–190 (190–191)[31]
7	–	–	52	253–254 (253–255)[17]
9	–	–	68	211–213 (212–214)[32,33]
11	–	–	68	110–113/1 (111–113/1)[34]

[a] Yields of isolated pure products.
[b] The products were characterized by comparison of their mps and spectral data with those reported in the literature.

study include conversion of 3-hydroxy-2-pyridinecarboxamide (**8**) and β-hydroxybutyramide (**10**), to 3-*H*-oxazolo[5,4-*b*]pyridin-2-one (**9**) (Scheme 3) and 5-methyl-2-oxazolidinone (**11**) (Scheme 4), respectively.

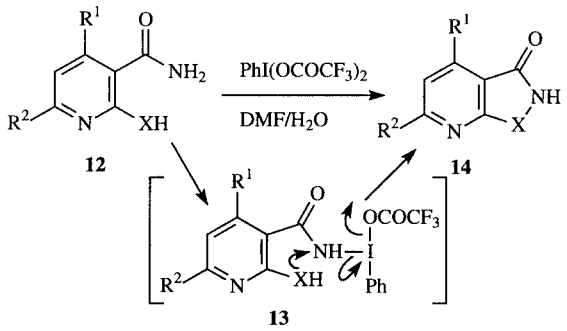


Scheme 3

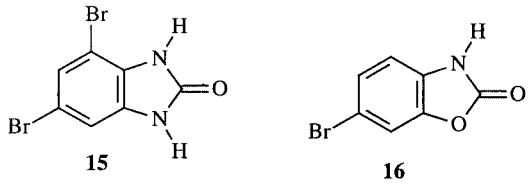


Scheme 4

Reddy et al.[19] have reported the synthesis of isoxazolo and pyrazolo pyridines **14** by the oxidation of 2-substituted 4-trifluoromethylpyridine-3-carboxamides **12** with IBTA in water and DMF (Eq. 3) without the formation of any rearranged 2-imidazolone or 2-oxazolone type products. This dichotomy can be explained by intramolecular interception of an intermediate in the HR reaction at a stage prior to rearrangement. This reaction sequence probably depends upon the stability of the intermediate **13** and may be reagent specific, i.e. $PhI(OCOCF_3)_2$-H_2O/DMF versus $PhI(OAc)_2$-KOH/MeOH.



Other I(III) mediated methods[11–14] for HR of amides applied to our compounds of general formula **1** did not yield the expected cyclized products (**1** → **3**). Beckwith and Dyall[20] have reported the first example of I(III) mediated cyclization of β-substituted amides involving HR. But their study focused on the construction of six-membered heterocyclic derivatives from the HR of 1,2-dicarboxamides. Using Br_2/KOH/MeOH (conventional conditions for HR of amides), anthranilamide (**4a**) and salicylamide (**4i**) yielded 4,6-dibromo-2-benzimidazolone (**15**) and 6-bromo-2-benzoxazolone (**16**), respectively. Obviously, ring closure was accompanied by aromatic substitution under the reaction conditions.



A plausible pathway for the formation of benzimidazolones and benzoxazolones probably involves in situ generation of isocyanate of general formula **2**, which undergoes intramolecular cyclization by participation of XH as nucleophile (Eq. 2).

Finally, the new hypervalent iodine oxidative method for the rearrangement of various β-substitued amides features i) good to high yields of the 2-benzimidazolones, 2-benzoxazolones and related compounds without aromatic substitution, and ii) an easy experimental procedure.

Melting points were taken in open capillaries and are uncorrected. Compounds **4c–h** were prepared by following the reported procedures.[21–23]

Benzimidazol-2-ones 5a−h and Benzoxazol-2-ones 5i, 5j and 7, 9, 11; General Procedure

Iodobenzene diacetate (IBD, 5 mmol) was added in portions to a stirred solution of appropriate carboxamide **4a−h, 4i, 4j, 6, 8, 10** (5 mmol) and KOH (560 mg, 10 mmol) in MeOH (20 mL) at 0−5 °C. The stirring was continued for about an hour till the IBD was consumed (TLC) (a solid separated out in several cases). The mixture was slowly neutralized with 1 N HCl and stirred with hexanes (10 mL) to remove iodobenzene. In most cases solid product thus separated was filtered and purified by recrystallization from a suitable solvent. In the other cases, the product was isolated by extraction (**5c, 9**) or column chromatography (**11**). The products were identified by comparing their melting points and spectral data with those reported in literature (Table).

4,6-Dibromo-2-benzimidazolone (15)

To an ice cold solution of anthranilamide (**4a**; 1g, 7.3 mmol) and KOH (823 mg, 14.7 mmol) in MeOH (25 mL) was added Br_2 (1.16 g, 7.3 mmol) dropwise and with vigorous shaking. The deep red colored mixture was allowed to stir for 2 h. The mixture was slowly neutralized with dil HCl to give a solid, which was filtered and recrystallized from EtOH to give pure **15**; mp >300 ° C (Lit.[35] mp 340 ºC).

MS: *m*/*z* = 288/290 (M^+).

6-Bromo-2-benzoxazolone (16)

Following the above procedure, salicylamide (**4i**) was converted to **16**; mp 218−220 ºC (Lit[36] mp 220 ºC).

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