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$BF_3{\cdot}OEt_2$-promoted reaction of isocyanides with *o*-aminobenzophenones

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ABSTRACT

Aliphatic isocyanides react with *o*-aminobenzophenones in dichloromethane under Lewis acid catalysis at ambient temperature to give, unexpectedly, 4-aryl-4-hydroxy-3,4-dihydroquinazolines in good to excellent yields. The outcome of the reaction is rationalized by a skeletal rearrangement of the initially formed 'intramolecular Passerini' reaction products, 2-amino-3-hydroxy-3-aryl-3*H*-indoles.

1. Introduction

Evolution of Ugi or Passerini reactions into their second-generation isocyanide-based multi-component variants is often based on one or several of the following logical premises: (i) replacing the electrophilic imine or carbonyl component with other electrophilic moieties;[1] (ii) replacing the isocyanide-intercepting carboxylate anion with other nucleophiles;[2] and (iii) combining the electrophilic moiety and the intercepting nucleophile within a single bifunctional reaction component and thus setting the stage for a ring-forming process.[3]

A primary amino group can effectively intercept an isocyanide which interacts with an appropriately positioned imine functionality. This was recently exemplified by the synthesis of 1,6-dihydropyrazine-2,3-dicarbonitriles from 2,3-diaminomalonitrile,[4] efficient assembly of 3,4,5,6-tetrahydropyrazine-2-amines from ethylenediamine,[5] and by the preparation of (1,4-dihydro)quinoxaline derivatives from *o*-phenylenediamines.[6] In such processes, both introducing an alternative nucleophile and exploiting the bifunctional character of the intermediate 'iminoamine' led to a reaction design that is quite novel, yet conceptually linked to the Ugi process (Scheme 1).

We became interested in exploring similar opportunities for performing the Passerini reaction on an aromatic ketone containing a strategically placed amino functionality to intercept the incoming isocyanide. A variety of *o*-acylanilines **1** are either commercially available or accessible by established methods (e.g., addition of Grignard reagents to anthranilonitriles[7]). We reasoned out that if we exposed **1** to isocyanide **2** under appropriate acid catalysis, a three-center, two-component Passerini-type reaction would be likely to occur and result in the formation of substituted 2-amino-3*H*-indol-3-ols **3** (Fig. 1). The 2-amino-3*H*-indol-3-ol moiety is present in a number of small molecules with CNS activity,[8] and specifically, is present (in its tautomeric form) in the structure of cyclazindol, a clinically used monoamine uptake inhibitor developed as an antidepressant[9] that was found to be an effective anorectic agent.[10]

2. Results and Discussion

We examined this reaction in a range of solvents and temperatures, with a variety of Brønsted and Lewis acids known to promote isocyanide-based multicomponent reactions (Table 1). The reactions were run by mixing *o*-aminobenzophenone and 4-methylbenzylisocyanide in an appropriate solvent, adding the acid catalyst and monitoring the reaction progress by LC–MS. To our delight, in all the cases studied, a product with $m/z = 329$ corresponding to the anticipated product **3a** was formed. While substantial formation of this product was achieved using stoichiometric amounts of Lewis acids such as $Yb(OTf)_3$ and $Zn(OTf)_2$, stoichiometric BF_3 diethyletherate was found to be superior in terms of both the purity of the product mixtures and the isolated yield of the $m/z = 329$ compound (entry 7). Notably, the principal products isolated from the reactions promoted by these three Lewis acids had identical ^1H and ^{13}C NMR spectra and contained the requisite signals corresponding to the expected structure **3a** (Fig. 1, $R^1 = R^2 = H$, $R^3 = 4\text{-}MeC_6H_4CH_2$).

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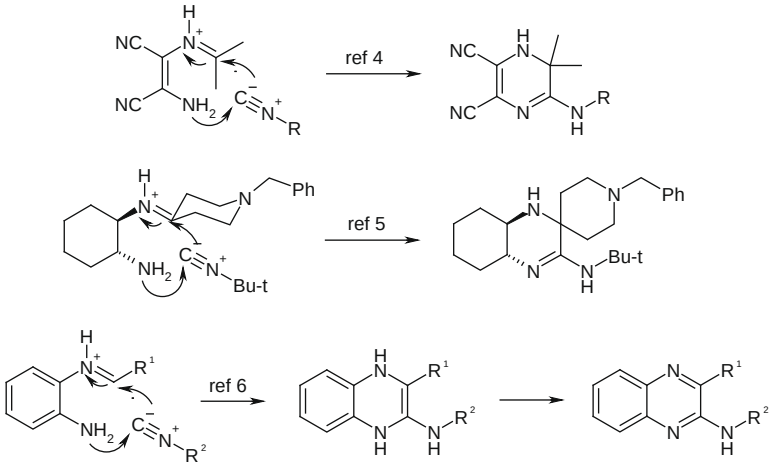


Scheme 1. Examples of a primary amino group playing the role of 'intercepting nucleophile' in second-generation isocyanide-based MCRs.

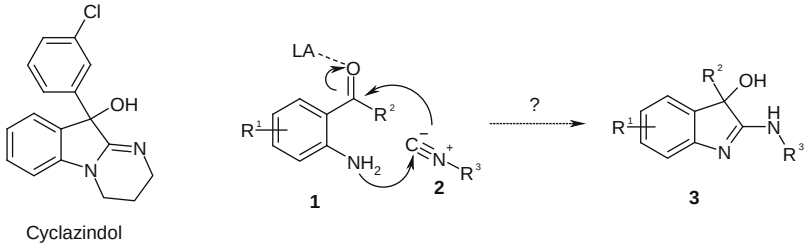
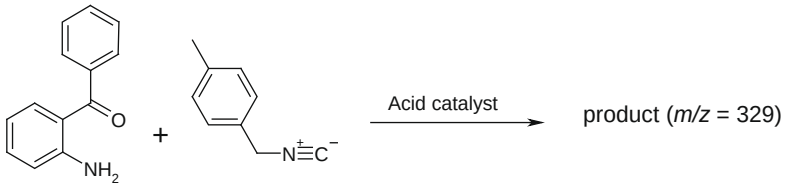


Figure 1. Structure of cyclazindol and the expected formation of 2-amino-3*H*-indol-3-ols **3** in the studied reaction.

Table 1
Conditions examined for the reaction of *o*-aminobenzophenone with 4-methylbenzylisocyanide



Entry	Acid catalyst (equiv)	Solvent	Temperature/reaction time	% of product in reaction mixture (LC–MS)	Isolated yield (%)
1	HCl (0.2)	MeOH	50 °C/24 h	<20	Not isolated
2	$HClO_4$ (0.2)	MeOH	50 °C/24 h	<20	Not isolated
3	NH_4Cl (1.0)	toluene	110 °C/30 h	<5	Not isolated
4	TMSCl (1.0)	MeCN	50 °C/16 h	<20	Not isolated
5	TMSCl (1.0)	MeCN/MeOH (9:1)	50 °C/16 h	<20	Not isolated
6	$BF_3{\cdot}OEt_2$ (0.2)	CH_2Cl_2	25 °C/18 h	~50	18
7	$BF_3{\cdot}OEt_2$ (1.0)	CH_2Cl_2	25 °C/8 h	~90	73
8	$Yb(OTf)_3$ (0.2)	CH_2Cl_2	25 °C/36 h	~30	Not isolated
9	$Yb(OTf)_3$ (1.0)	CH_2Cl_2	25 °C/16 h	~70	35
10	$Zn(OTf)_2$ (0.2)	CH_2Cl_2	25 °C/36 h	<20	Not isolated
11	$Zn(OTf)_2$ (1.0)	CH_2Cl_2	25 °C/18 h	~50	27

However, when we proceeded to confirm the structure of the product by single-crystal X-ray analysis, we found that the compound was 3-(4-methylbenzyl)-4-phenyl-3,4-dihydroquinazolin-4-ol (**4a**), that is, formally, the product of a [4+2] (and not [4+1] as initially expected) ring forming process (Fig. 2). In order to distinguish the spectral characteristics of **4a** (and of the subsequently synthesized 3,4-dihydroquinazolin-4-ols **4**) from those of the initially expected 2-[(4-methylbenzyl)amino]-3-phenyl-3*H*-indol-3-ol **3a**, we prepared an authentic sample of **3a** using the literature protocol[11] (Scheme 2). Indeed, the NMR spectra of **3a** were found to be different from those of **4a** (specifically, in the relative positions of the signals in the ^{13}C NMR spectrum, for example, the 'amidine' carbon atom of **3a** at 176.5 ppm, see Supplementary data).

The formation of the 3,4-dihydroquinazolin-4-ol **4a** can be *tentatively* rationalized by the initial formation (via 'intramolecular Passerini' reaction) of the molecular framework of **3a** followed by

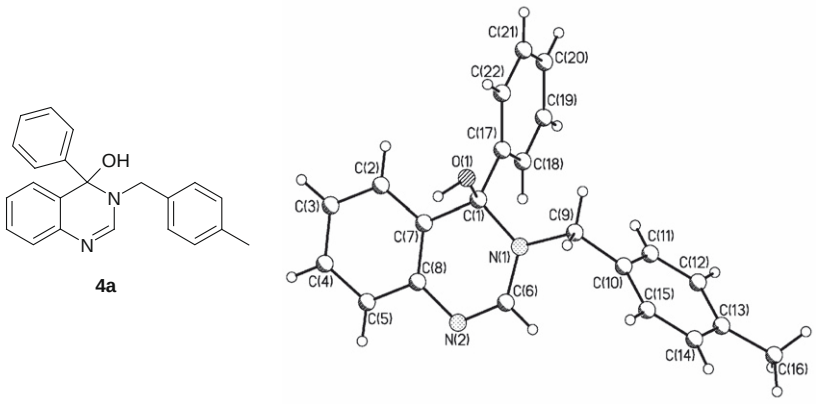
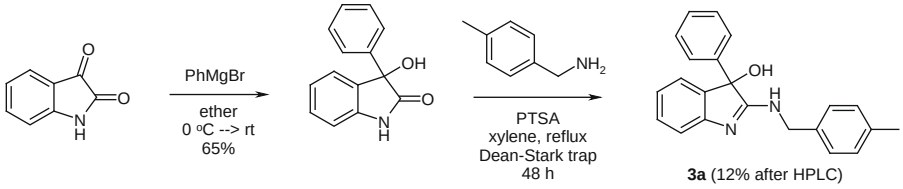
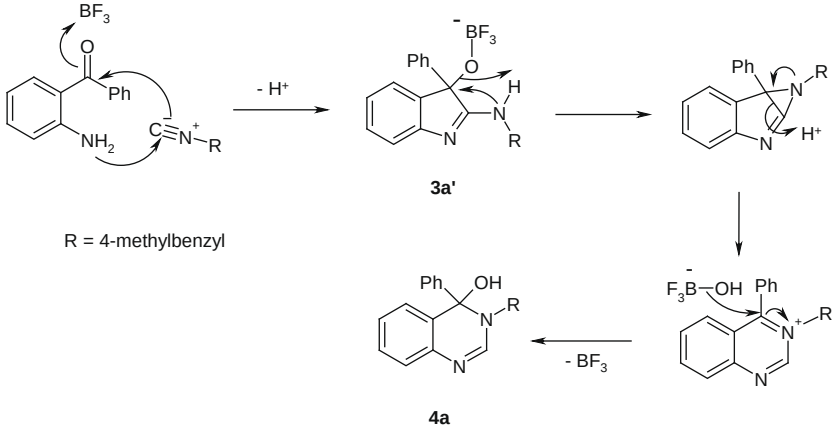


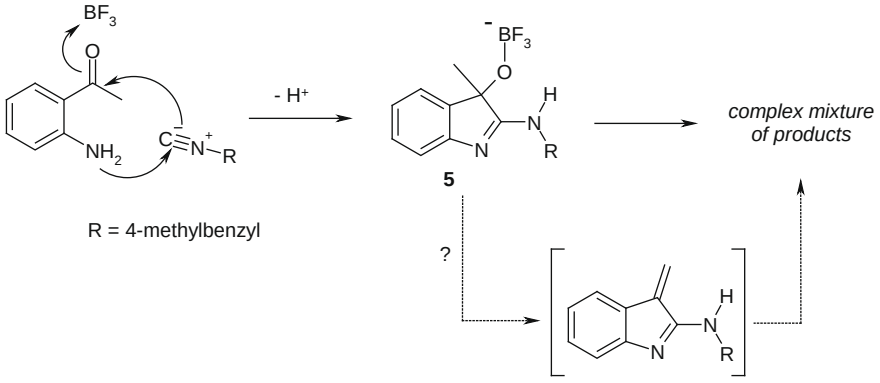
Figure 2. Structure of **4a** as confirmed by single-crystal X-ray analysis.



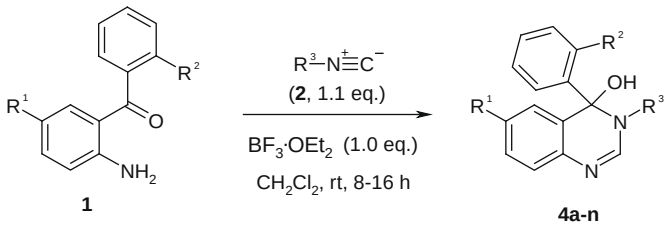
Scheme 2. Preparation of **3a** according to the literature.[11]



Scheme 3. Proposed reaction mechanism for the synthesis of **4a**.



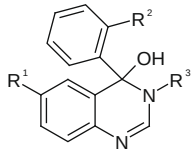
Scheme 4. Attempted reaction between *o*-acetylaniline and 4-methylbenzylisocyanide.



Scheme 5. Synthesis of 3,4-dihydroquinazolin-4-ols **4** described in this work.

in situ skeletal rearrangement into **4a** as proposed in Scheme 3. The following observations support the plausibility of this tentative mechanism: (i) the overall process is promoted efficiently by the strong Lewis acidic boron trifluoride, the 'oxophilic' character of which is required for the formal dehydration of **3a**′; (ii) milder Lewis acids (especially Brønsted acids) do not promote this process efficiently, probably due to their inability to trigger the skeletal rearrangement of **3a**′; (iii) the preparative yield for **3a** (Scheme 2) was quite low despite the promising claims in the literature,[11b] most likely due to significant ring strain in the 2-amino-3-phenyl-

Table 2
3,4-Dihydroquinazolin-4-ols **4** synthesized in this work



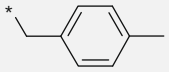
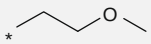
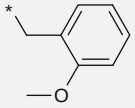
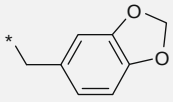
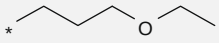
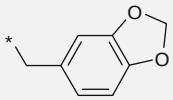
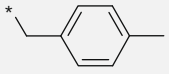
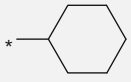
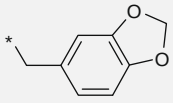
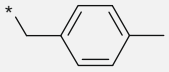
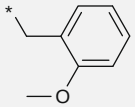
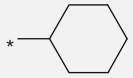
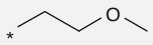
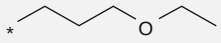
Compound	R^1	R^2	R^3	Isolated yield (%)
4a	H	H		73
4b	H	H		85
4c	H	H		41
4d	H	H		66
4e	H	H		67
4f	Cl	Cl		82
4g	Cl	Cl		65
4h	Cl	Cl		65
4i	Cl	H		77
4j	Cl	H		88
4k	Cl	H		50

Table 2 (*continued*)

Compound	R^1	R^2	R^3	Isolated yield (%)
4l	Cl	H		54
4m	Cl	H		78
4n	Cl	H		67

3*H*-indol-3-ol structure; relieving this strain could be a substantial driving force for the proposed skeletal rearrangement; (iv) when a similar reaction was attempted with *o*-acetylaniline, a complex mixture of unidentified products was obtained (Scheme 4); this is possibly due to an alternative pathway existing for the dehydration of **5**; and (v) the present reaction does not work with aromatic isocyanides (vide infra): according to the mechanism, the lone pair of the exocyclic nitrogen atom would not be available to participate in the rearrangement process for intermediates such as **3a**′ bearing aromatic R groups.

We attempted to probe the mechanism by exposing **3a** to 1 equiv of $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature. Shortly after the addition of the Lewis acid, a precipitate formed that remained unchanged on stirring the reaction mixture for 72 h. Upon basic aqueous work-up, **3a** was fully recovered and no trace of **4a** was detected. These observations are the likely result of boron trifluoride complexation to the 'amidine' moiety of **3a** (and not to the sterically encumbered hydroxy group). This, in our opinion, does not contradict the proposed tentative mechanism: the skeletal rearrangement of **3a**′ is triggered by boron already complexed to the oxygen atom as a result of the preceding three-center two-component reaction with the isocyanide and indeed, can occur only in the course of the reaction. However, further studies are needed to provide more evidence for the plausibility of the proposed mechanism.

We prepared several other 3,4-dihydroquinazolin-4-ols **4** from commercially available *o*-aminobenzophenones **1** and isocyanides **2** (Scheme 5, Table 2). Notably, we found that this reaction did not proceed with aromatic isocyanides, which is consistent with the proposed reaction mechanism (vide supra). The isolated yields of **4a**–**n** were moderate to good and all the products were characterized by ^1H and ^{13}C NMR spectroscopy, LC–MS and elemental analyses; X-ray analysis was also performed on representative compound **4e** to confirm the generality of the reaction (see Supplementary data).[12]

3,4-Dihydroquinazolin-4-ols are not well represented in the literature. They have been isolated and characterized as metabolites of hypoglycemic 5-phenyl-1,3,4-benzotriazepines.[13] The chemical syntheses of 3,4-dihydroquinazolin-4-ols[14,15] are quite elaborate which may explain the scarcity of the literature reports. We expect these compounds to serve as bioisosteric replacements for the CNS-active 3*H*-indol-3-ols and hope that their rapid synthesis described herein will lead to more extensive biological evaluation of the 3,4-dihydroquinazolin-4-ol scaffold.

In conclusion, we have described a novel $BF_3{\cdot}OEt_2$-promoted reaction of *o*-aminobenzophenones with aliphatic isocyanides. Contrary to expectations, hitherto poorly described 3,4-dihydroquinazolin-4-ols were formed as products. A tentative mechanism requiring an initial three-center, two-component Passerini-type reaction with subsequent skeletal rearrangement of the 3*H*-indol-3-ol framework has been proposed.

3. Typical procedure

3.1. Synthesis of 3,4-dihydroquinazolin-4-ols 4

A solution of *o*-aminobenzophenone **1** (5 mmol) and isocyanide **2** (5.5 mmol) in CH_2Cl_2 (25 mL) was treated with $BF_3{\cdot}OEt_2$ (5.0 mmol) and the resulting mixture was stirred at rt for 8–16 h. The reaction mixture was washed with 5% aqueous NaOH (10 mL) and H_2O (2 × 10 mL). The combined aqueous solutions were back-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The products were purified either by crystallization from MeOH or by chromatography on silica gel using 5% MeOH in CH_2Cl_2 as eluent.

3.2. 3-(4-Methylbenzyl)-4-phenyl-3,4-dihydroquinazolin-4-ol (4a)

Beige solid, mp = 145–147 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 7.43 (d, J = 5.2 Hz, 2H), 7.33 (m, 2H), 7.25 (d, J = 5.2 Hz, 2H), 7.15 (m, 1H), 7.03–7.11 (m, 5H), 6.93 (m, 2H), 4.17 (ABq, $\Delta\nu$AB = 14.3 Hz, J = 11.6 Hz, 2H), 3.32 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 147.6, 146.0, 140.9, 136.3, 135.2, 128.8, 128.7, 128.2 (2 signals), 128.0, 127.9, 127.5, 126.4, 124.0, 123.9, 84.3, 48.8, 20.7; LC–MS (M+H) 329. Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.51; H, 6.19; N, 8.55.

Acknowledgment

We would like to thank Dr. Alexander Manaev of Chemical Diversity Research Institute for his help in obtaining X-ray crystallographic data.

Supplementary data

Supplementary data (characterization data for the newly synthesized compounds (**3a**, **4a**–**n**), X-ray crystallographic files (CIF) for compounds **4a** and **4e**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.031.

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12. Crystallographic data (excluding structure factors) for the structures **4a** and **4e** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 739159 and 739160. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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