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Rapid, robust, clean, catalyst-free synthesis of 2-halo-3-carboxyindoles

Aaron R. Kunzer *, Michael D. Wendt

Cancer Research, Global Pharmaceutical R&D, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6101, United States

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ABSTRACT

A novel synthesis of 2-halo-3-carboxyindoles from 2-(2,2-dihalovinyl)anilines was discovered. Reaction conditions and substrate applicability were studied. Optimally, the reaction takes only minutes when these substrates are heated in DMSO at 120 °C in the presence of cesium carbonate. However, the reaction is robust and takes place at a wide range of temperatures, is tolerant of aqueous reaction conditions, and can be performed in a variety of polar solvent/carbonate base combinations—where the limiting factor is base solubility. A wide range of substituents is tolerated on the 2-(2,2-dihalovinyl)anilines, and yields are generally high, requiring only acidic aqueous work-up to obtain pure products. No catalyst is required for the transformation. The mechanism is believed to involve initial formation of an alkynyl bromide intermediate followed by ring closure and carbon dioxide trapping, leading to product formation.

In the course of our drug discovery work, we were exploring potential routes to oxindoles under mild conditions. We were curious if the known conversion of (2,2-dibromovinyl)benzenes to phenylacetylamides[1] shown in Scheme 1 might provide such a route if applied intramolecularly. We were, however, skeptical due to the fact that the alkynamine intermediate, 2-3-indolyne, is unlikely to form in this case (Scheme 1).[2]

Upon running an initial test reaction with **1a** (synthesized via Corey–Fuchs olefination of 2-nitrobenzaldehyde followed by reduction of the nitro group), the 2-bromo-3-carboxyindole **2a** was cleanly isolated in high yield via aqueous acidic work-up only (Scheme 2). Production of this disubstituted indole derivative seemed to be a very interesting and promising result.

2-Chloro and 2-bromoindoles can undergo nucleophilic substitution reactions at the 2-position[3] as well as a variety of typical cross-coupling reactions including Suzuki,[4] Heck,[5] Stille,[6] Sonogashira,[7] carboxylation,[8] and C–H activation coupling.[9] Further, 2-halo-3-carboxyindoles have historically been synthesized by subjecting oxindoles to Vilsmeier–Haack reaction conditions followed by oxidation of the resulting 2-halo-3-carboxaldehydes with strong oxidants such as $KMNO_4$ or $NaClO_2$.[3b,10] This methodology obviously limits the functional groups that can be present in the substrate. Additionally, attempts to synthesize 2-bromo-3-carboxyindoles via bromination have had limited success. First, the brominations were performed on esters rather than directly on the acids, and second, there are no examples of clean, selective bromination at the 2-position of N-unsubstituted indoles in the literature.[11]

We immediately undertook a study to examine the effects of various solvent systems and temperatures on the transformation (Table 1). It should be noted that in all cases, pure product was isolated by aqueous acidic work-up alone. The results demonstrated that more polar solvents generally performed well, with the exception of NMP (entry 2). DMSO (entry 1) appeared to be the most effective solvent tested, likely due to increased base solubility, and 1,4-dioxane (entry 5) proved ineffective. Reaction temperature (entries 8 and 9) did not affect yields. Most interesting was the anhydrous run included in the study (Table 1, entry 10). Cs_2CO_3 in DMSO was used to maximize base solubility and the reaction time was significantly shortened to 45 min compared to 6 h for the analogous aqueous condition (entry 1). Thus, it appears that while the reaction can tolerate the presence of water with no deleterious effects on product purity or yield, the reaction rate increases in the absence of water.

With the discovery of the improved anhydrous reaction conditions, we sought to investigate various aspects of the base in the reaction as well as revisiting the effects of temperature (Table 2). Reducing the equivalents of base in the reaction (entries 4 and 5) slows the rate, but appears to have no effect on yield, further establishing the robustness of the reaction. The use of K_2CO_3 as base (entry 6) also slowed the reaction rate, but the addition of 18-crown-6 to improve base solubility under the same conditions (entry 7) restored the rate to equivalence with the use of Cs_2CO_3. In both cases, the use of K_2CO_3 did not adversely affect the high yields of the reaction. In general, conditions increasing the rate of reaction (higher temperature, better base solubility) also seem to improve yields.

Given the ease of indole formation under the reaction conditions, we sought to determine if the analogous 2-bromo-3-carboxybenzofuran and benzothiophene could be formed in the

* Corresponding author. Tel.: +1 847 935 2363; fax: +1 847 938 1004.
E-mail address: aaron.kunzer@abbott.com (A.R. Kunzer).

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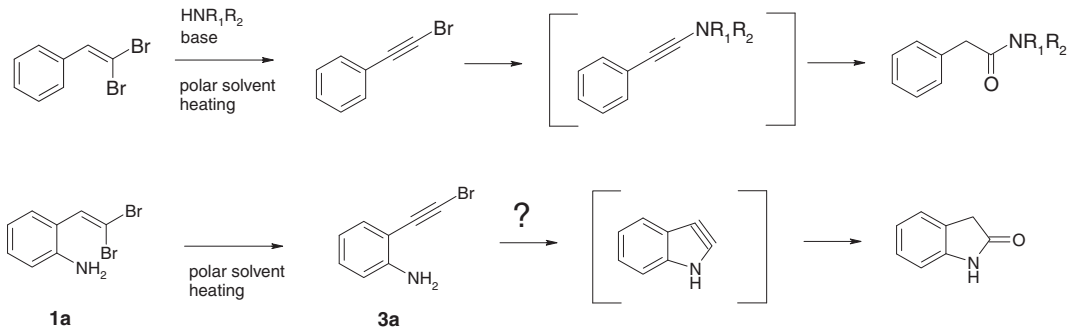


Scheme 1. Known conversion of (2,2-dibromovinyl)benzene to amides and analogous intramolecular reaction mechanism.

Scheme 2. Initial test reaction.

Table 1
Solvent/temperature study[a]

Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	DMSO	100	6	79
2	NMP	100	23[c]	25
3	DMF	100	12	71
4	Ethylene glycol	100	4	65
5	1,4-Dioxane	100	48	0[d]
6	DMSO[e]	100	5	85
7	DMSO[f]	100	6	86
8	DMSO	80	24	85
9	DMSO	120	2	91
10	DMSO[g]	100	45 min	73

[a] Standard conditions: dibromoalkene 0.5 mmol, 3 equiv Na_2CO_3 (3 M solution, 0.5 mL), solvent 1.5 mL (solvent/water = 3:1).
[b] Isolated yields.
[c] Reaction not complete, but stopped and isolated product.
[d] Trace by LC/MS.
[e] DMSO/water, 2:1 (2 mL total solvent volume maintained).
[f] DMSO/water, 4:1 (2 mL total solvent volume maintained).
[g] Anhydrous conditions: 3 equiv Cs_2CO_3, 2 mL DMSO.

Table 2
Anhydrous temperature/base study[a]

Entry	Base	Equiv Base	Temp (°C)	Time (min)[b]	Yield[c] (%)
1	Cs_2CO_3	3	100	45	73
2	Cs_2CO_3	3	80	6 h	70
3	Cs_2CO_3	3	120	8[d]	87
4	Cs_2CO_3	2	120	10	81
5	Cs_2CO_3	1	120	60	83
6	K_2CO_3	3	120	45	85
7	K_2CO_3[e]	3	120	5	93

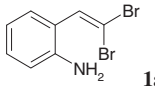
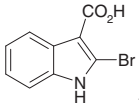
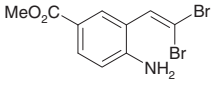
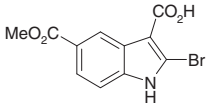
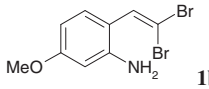
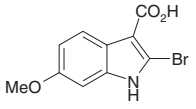
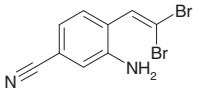
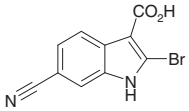
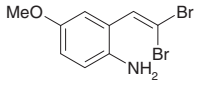
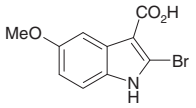
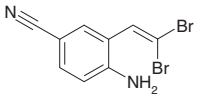
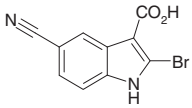
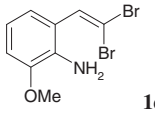
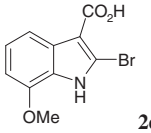
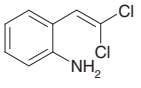
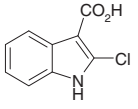
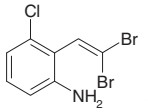
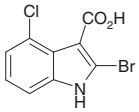
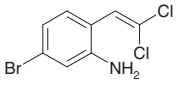
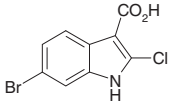
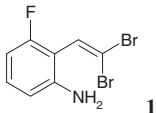
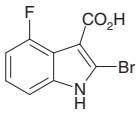
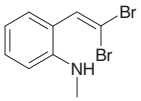
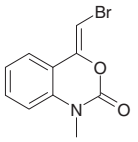
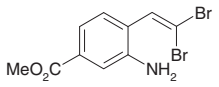
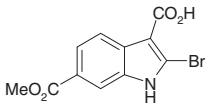
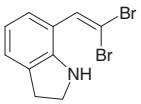
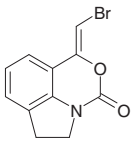
[a] Standard conditions: dibromoalkene 0.5 mmol, 3 equiv base, DMSO 2.0 mL
[b] Times minimized.
[c] Isolated yields.
[d] Only trace of SM at 5 min by LC/MS.
[e] Added 6 equiv 18-crown-6.

same manner. It is known that 2-bromobenzofurans and 2-bromobenzothiophenes can be synthesized from their respective (2,2-dibromovinyl)benzenes via intramolecular cross-coupling.[12] 2-Bromobenzofurans can also be synthesized from corresponding (2,2-dibromovinyl)benzenes by treatment with base alone.[13] However, this transformation appears to be specific to indoles. No desired products were observed in either case, with the reaction conditions leading to decomposition of the 2,2-dibromovinyl substrates.

In order to establish the scope of the reaction, we evaluated numerous substrates (Table 3). In general yields were high with the exception of **1c**, which unsurprisingly, rapidly oxidized. Both electron-donating (**1b–d**) and electron-withdrawing groups (**1g–j**) were tolerated at various ring positions. In addition, some degree of steric hindrance (**1d–e**) was not detrimental to the transformation. 2,2-Dichlorovinyl substrates also cleanly underwent the transformation to yield the corresponding 2-chloro-3-carboxyindoles (**1k–l**). Interestingly, N-substituted substrates (**1m–n**) did not produce the expected 1-substituted indole products. Instead, the cyclic carbamate, 4-[1-Bromo-meth-(*Z*)-ylidene]-1,4-dihydrobenzo[*d*][1,3]oxazin-2-one, products **2m** and **2n** were produced in low yield. As these reactions were much less clean, products had to be isolated by flash column chromatography. However, this was another interesting result as examples of this chemotype in the literature are limited to a few references, and have historically been synthesized by either subjecting isatoic anhydrides to Wittig[14]/Horner–Wadsworth–Emmons[15] chemistry or via enolate formation of amino acetophenones.[16] In fact, there are no examples of alkenyl halides such as these in the literature that would allow for further cross-coupling chemistry and derivative generation.

To elucidate the mechanism of the indole formation, we started with the observation that at reaction temperatures lower than 120 °C, the slower reaction rate of **1a** allowed an intermediate to be observed by LC/MS. The mass of this intermediate corresponded to the mass of the alkynyl bromide **3a** that would be formed by first abstracting the benzylic proton (Scheme 1). Since it is known that under basic conditions these alkynyl bromides and chlorides form from their corresponding 2,2-dihalovinyl compounds,[17] it would be logical to propose that the first step of the reaction is alkynyl halide formation. To prove this, we used the anhydrous reaction conditions, but ran the reaction at 80 °C. This allowed us to observe the formation of a large amount of intermediate by LC/MS, stop the reaction before completion, and isolate this intermediate. NMR and LC/MS comparison of a sample of **3a** generated by treatment of **1a** with DBU confirmed that the intermediate was, in fact, **3a**. Further, we subjected **3a** to the standard reaction conditions, and **2a** was obtained in 77% yield. At this point, we could confidently propose a mechanism for indole formation (Fig. 1). The mechanism begins with alkynyl halide generation followed by ring closure and trapping of CO_2 present in solution due to the carbonate base. This mechanism has support in the literature as base-catalyzed alkyne cyclizations are a well established indole synthesis technique.[18] Alkyne cyclizations to indoles with

Table 3
Substrate study under standard anhydrous conditions[a]

Substrate	Product	Yield[b] (%)	Substrate	Product	Yield[b] (%)
 **1a**	 **2a**	87	 **1h**	 **2h**	81
 **1b**	 **2b**	79	 **1i**	 **2i**	85
 **1c**	 **2c**	40	 **1j**	 **2j**	65
 **1d**	 **2d**	67	 **1k**	 **2k**	95[c]
 **1e**	 **2e**	74	 **1l**	 **2l**	80
 **1f**	 **2f**	84	 **1m**	 **2m**	22[c]
 **1g**	 **2g**	73	 **1n**	 **2n**	18

[a] Standard conditions: dibromoalkene 0.5 mmol, 3 equiv Cs_2CO_3, DMSO 2.0 mL, 120 °C, 10 min. unless otherwise noted.
[b] Isolated yields.
[c] Reaction time 20 min.

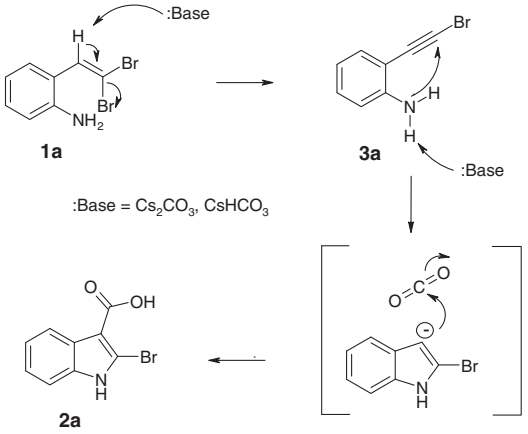


Figure 1. Proposed mechanism for indole formation.

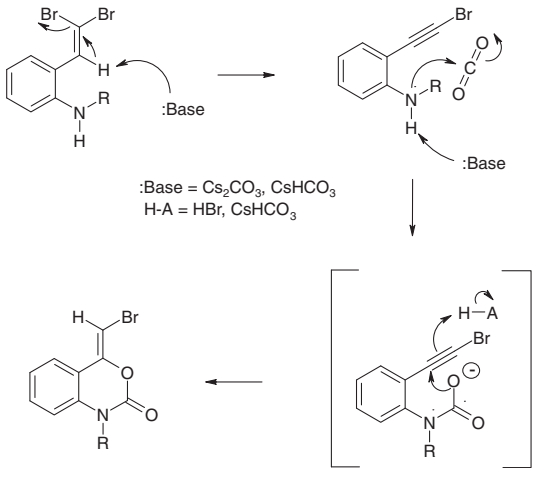


Figure 2. Proposed mechanism for cyclic carbamate formation.

accompanying carboxylation at the 3-position are also known, albeit using transition metal catalysts with trapping of CO in the presence of an alcohol.[19] Base-catalyzed alkyne cyclization with subsequent CO_2 trapping has, however, been demonstrated in the synthesis of benzofurans,[20] and recently carboxylation of aromatic heterocycles has been achieved using a combination of CO_2 and Cs_2CO_3 in hot DMF.[21]

The proposed mechanism of cyclic carbamate formation, as shown in Figure 2, starts similarly, as **3a** is also readily formed in

the reaction. In the case of **1m**, a LC/MS sample taken at 10 min showed a significant amount of alkynylbromide present in the reaction mixture. The presence of the methyl group in **1m** and the ring constraints of **1n** may slow attack of the anilino N on the alkynyl bromide, allowing the well-established base-catalyzed CO_2 trapping by the anilino N to become significant.[22] This forms an intermediate that can be quickly trapped by attacking the alkynyl bromide group at the benzylic position. Nucleophilic attack at this position has been demonstrated previously.[23] Further, the geometry of this attack explains why only the *Z*-isomer products are observed.

In summary, we have developed a novel synthesis for 2-halo-3-carboxyindoles by heating (2,2-dihalovinyl)arenes in DMSO in the presence of carbonate base. The reaction is fast and robust to a wide range of reaction conditions and substrates. The broad functional group tolerance of this transformation is a significant improvement over the historical Vilsmeier–Haack/oxidation methodology and produces clean products in high yields that can be easily isolated by simple aqueous work-up. This reaction offers a novel way to make synthetically important fluorinated indoles, differentiated bis-carboxy indoles, and mixed halogen indoles, which can serve as an entry for both selective and successive cross-coupling chemistries. Recently, the palladium-catalyzed synthesis of 2-bromoindoles, including mixed halogen indoles, was reported.[24] Our synthesis eliminates the need for palladium and the added presence of the 3-carboxy group allows the products described here to be employed as stable synthons for their corresponding 3-H analogs. Thus, potentially unstable 2-haloindoles are stabilized and can be readily decarboxylated if desired.[25] In addition, we have discovered a stereospecific synthetic route to the novel 4-[1-bromo-meth-(*Z*)-ylidene]-1,4-dihydro-benzo[*d*][1,3]oxazin-2-ones, and an investigation of optimized reaction conditions for this underexplored chemotype is ongoing. Given the substantial importance of indoles in both organic and medicinal chemistry, we believe this novel transformation will find broad use in the synthesis of functionalized indoles.

Acknowledgments

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Supplementary data

Supplementary data (representative procedures and NMR spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.037.

References and notes

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