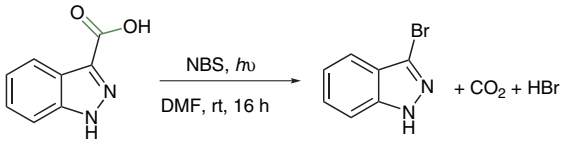
Decarboxylative Bromination of Hetarenes: Initial Mechanistic Insights

Pritesh R. Patel[a]
Scott H. Henderson[b]
Mark S. Roe[c]
Mark A. Honey*[d]

[a] School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton, WV1 1LY, UK
[b] Sussex Drug Discovery Centre, University of Sussex, Brighton, BN1 9RH, UK
[c] School of Life Sciences, University of Sussex, Brighton, BN1 9RH, UK
[d] School of Science, Faculty of Engineering and Science, University of Greenwich, Chatham, Kent, ME4 4TB, UK
m.a.honey@gre.ac.uk



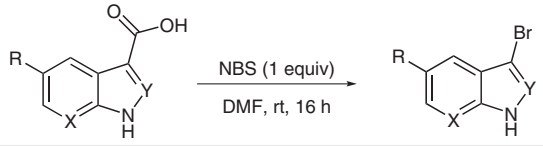
- substrate activation of NBS
- light sensitive
- potential radical pathway

Abstract After an initial report from our laboratory describing metal-free decarboxylative halogenation of various azahetarenes, we set out to investigate the possible mechanism by which this chemistry occurs. Evidence from this mechanistic investigation suggests that this chemistry occurs via a radical pathway, with ^{1}H NMR studies suggesting that the acidic substrates activate NBS.

Key words decarboxylation, halogenation, reaction mechanism, bromosuccinimide, azahetarenes

The manipulation of heterocyclic compounds to modulate or change their reactivity is of fundamental importance to a vast range of chemical industries.[1,2] To be able to introduce new functionality selectively under mild conditions is something that numerous academic and industrial research groups strive to achieve. The ability to halogenate aromatic/hetaromatic compounds selectively can be an essential element in the synthesis of pharmaceutically active molecules within drug-discovery programmes[3–5] or it can create handles for easy manipulation of functionality when investigating structure–activity relationships during lead optimization.[6,7]

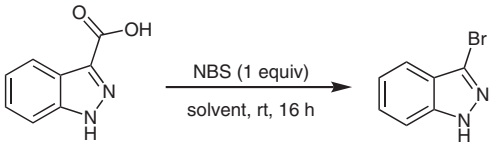
A major method employed to introduce halogens selectively onto aromatic and aliphatic substrates employs decarboxylative halogenation. This area of research has a rich history, but the greatest advances have mainly been achieved by using alkanoic acids as substrates.[8] There are several reported methods for performing decarboxylative halogenation on aromatic substrates, but they often rely on metal catalysts, require high reaction temperatures, or are unselective.[9–11] Recent reports by Larrosa and co-workers have advanced this area of research, but their method requires stoichiometric quantities of a base and relatively high reaction temperatures.[12,13] We recently reported a metal-free selective decarboxylative halogenation of hetaromatic compounds under mild conditions (Scheme 1).[14] We found that indole-, indazole-, azaindole-, and azaindazolecarboxylic acids underwent spontaneous decarboxylative bromination in the absence of any catalyst or initiator. To exploit this chemistry further, we needed to understand the mechanism by which this reaction occurs. Previous reports by the Larrosa group indicated that, under their basic conditions with aromatic substrates, decarboxylative halogenation probably proceeds by a concerted mechanism.[12,13] As we believed it was possible for the mechanism of our chemistry to proceed by a radical pathway or by a concerted pathway, we set out to determine experimentally which pathway was the most likely.



Scheme 1 Decarboxylative halogenation of azaheterocycles[14]

Having previously established that the decarboxylative bromination of indazolecarboxylic acids occurs spontaneously in DMF in the presence of NBS,[14] we next sought to investigate whether this reaction was able to proceed in a range of solvents (Table 1). We found that the reaction is tolerant of polar protic and polar aprotic solvents, although lower yields are obtained for solvents in which the solubility of the starting material appears to be poor. Mixed solvent systems were also investigated, but did not provide any improvement on the standard conditions employing DMF. Because DMF still appeared to be the best solvent for this chemistry, we used it in all our initial mechanistic studies.

Table 1 Investigation of Solvent[15]

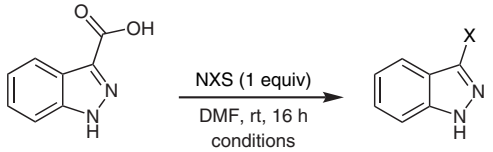


Entry	Solvent	Yield (%)
1[16]	DMF	67
2	EtOAc	56
3[a]	CH_2Cl_2	17
4	MeOH	37
5[a]	H_2O	0
6[a]	MeCN	37
7[a]	toluene	23
8[a]	Et_2O	trace
9	$CHCl_3$	trace
10	MeOH–H_2O	trace
11	CH_2Cl_2–EtOAc	trace

[a] Solubility issues were observed.

Having established that 1*H*-indazole-3-carboxylic acids undergo spontaneous decarboxylative bromination in the presence of NBS at room temperature, we sought to investigate the mechanism by which this transformation occurs. Our general procedure for this chemistry started with the addition of the acidic substrate to the reaction solvent. Once the substrate had dissolved, often giving a colourless solution, NBS was added. It was at this point that we observed an instant change in the colour of the reaction mixture: the mixture typically turned yellow, brown, or red. Our belief, supported by ^{1}H NMR spectroscopic evidence detailed later, is that the acidic substrate activates NBS towards dissociation, and so quickly forms a low concentration of bromine. As bromine can react by an electrophilic or a radical pathway, our next thought was to investigate whether the bromine in the reaction mixture reacts with the substrate by either of these pathways. Our initial efforts focused on the effect of light on our reaction system, as bromine is known to be activated by the presence of light. Entries 1 and 3 in Table 2 show the isolated yields of 3-bromo-1*H*-indazole[16] from reactions performed in DMF at room temperature in the presence of ambient light and in darkness, respectively. All experiments were conducted with new reaction vials and stirrer bars to avoid the introduction of any trace metals from previous chemistry. It is clear that the presence of light significantly increases the overall yield of the brominated product compared with that of the reaction conducted in the dark. It is known that in the presence of light bromine typically undergoes homolytic cleavage to form bromine radicals.[17] Therefore, to probe the mechanism further, we investigated whether free radicals are involved in this chemistry by adding the radical quencher 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) to our reaction mixture, both in the presence of ambient light and in darkness. Notably, even in the presence of the radical quencher TEMPO, the initial instant colour change of the reaction mixture was observed, and therefore the suspected initial bromine formation still occurred. When TEMPO was present in reactions conducted in ambient light and in darkness (entries 2 and 4), the reaction failed to proceed, with only the starting material being recovered. The suppression of the reaction in the presence of the radical quencher suggests a fundamental involvement of free radicals in the progress of this reaction. Having established that the presence of TEMPO in the reaction mixture for the chemistry with NBS stopped the reaction from proceeding, the effect of TEMPO on the progress of the reaction in the presence of NCS was investigated. Although the isolated yield of 2-chloro-1*H*-indazole (entry 5) was low, the reaction was able to proceed under the standard conditions. However, as with the case for the chemistry with NBS, the addition of TEMPO appeared to prevent any reaction from occurring (entry 6).

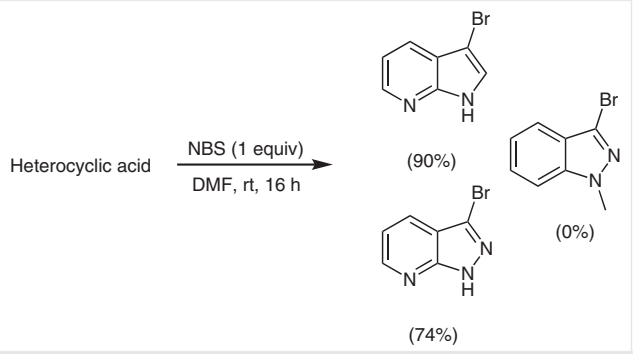
Table 2 Effect of TEMPO on the Progress of the Reaction



Entry	Halogen	Conditions	TEMPO (equiv)	Yield[a] (%)
1	Br	ambient light	0	65
2	Br	ambient light	2	trace
3	Br	foil-covered vessel	0	38
4	Br	foil-covered vessel	2	0
5	Cl	ambient light	0	12
6	Cl	ambient light	3	0

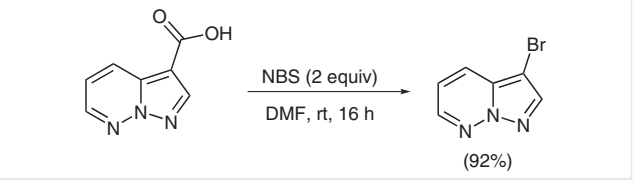
[a] Isolated yield.

In our previous report,[14] we described the utility of this reaction for several azaheterocycles, including the three examples shown in Scheme 2. We found that, in general, more-electron-deficient heterocycles showed greater reactivity, and good yields of halogenated azaindoles and azaindazoles were obtained. Although the relatively electron-deficient indazole-3-carboxylic acid readily underwent halodecarboxylation, the reaction failed to proceed when the indazole was N-methylated. This raised the question of whether a free N–H is needed for this reaction to proceed or the failure to react is the result of an electronic effect.



Scheme 2 Current scope of method[14]

As part of an ongoing project, we subjected pyrazolo[1,5-*b*]pyridazine-3-carboxylic acid to our standard conditions (Scheme 3), and we found that the reaction proceeded smoothly to give the desired brominated product in excellent yield, with the structure of the product being confirmed by single-crystal X-ray crystallography (Figure 1).[18] Although the heterocyclic core was slightly different, this reaction proceeded in the absence of a free N–H group, suggesting that its presence might not be important for certain substrates in the mechanism of this reaction.



Scheme 3 Decarboxylative bromination of pyrazolo[1,5-*b*]pyridazine-3-carboxylic acid

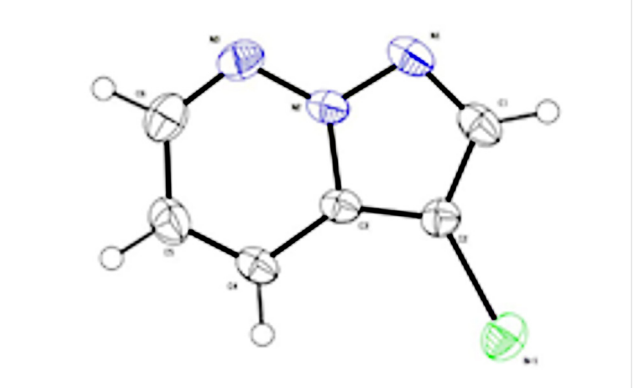
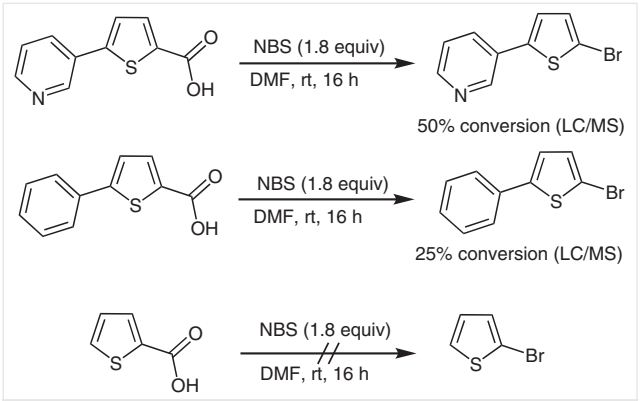


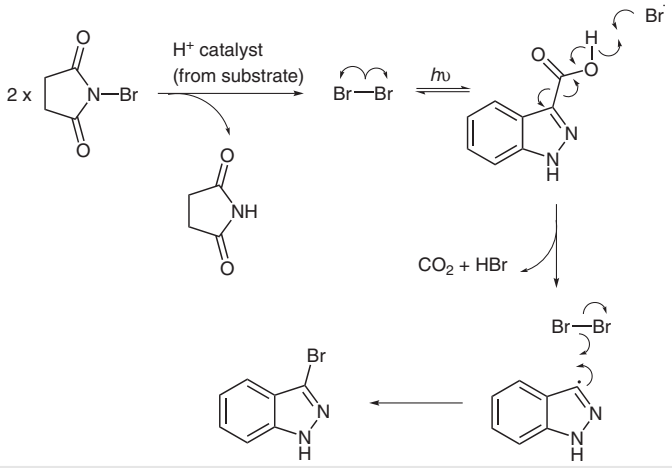
Figure 1 X-ray crystal structure of 3-bromopyrazolo[1,5-*b*]pyridazine[18]

As part of a continuing medicinal chemistry project, decarboxylative bromination has formed an integral step in the synthesis of compounds with potential biological activity. Decarboxylative bromination of substituted thiophenes also proved successful (Scheme 4), although the products were not isolated as they were obtained only transiently and reacted in situ as part of a drug-discovery programme. Unfortunately, the use of unsubstituted thiophene-2-carboxylic acid proved unsuccessful, with no product being observed. Although disappointing, this result also adds weight to the argument that electron deficiency of the aromatic ring, and the ability to stabilize a free radical facilitates this reaction.



Scheme 4 Decarboxylative bromination of thiophenes

To investigate the possible mechanism further, the standard reaction was studied by ^{1}H NMR spectroscopy in deuterated DMF. NBS has been known to react with numerous solvents,[19] so we first investigated the possibility of activation of NBS by DMF-d_7. NBS was dissolved in DMF-d_7 and left at room temperature for 30 minutes. Had NBS reacted with DMF, the resultant ^{1}H NMR of the reaction mixture would have shown a mixture of compounds. However, the ^{1}H NMR showed only one peak for the four equivalent aliphatic protons of NBS, and no evidence could be found for the existence of the N–H corresponding to the formation of succinimide. This suggests that, although DMF acts as a solvent and interacts with NBS in this regard, it does not appear to alter its reactivity significantly. It has been reported that *N*-halosuccinimides can be activated by both Brønsted[20] and Lewis acids,[21] the lone pair of electrons on the carbonyl oxygen acting as a Lewis base. Protonation of the carbonyl oxygen results in a weaker N–Br bond, and so increases the rate of dissociation. As NBS appeared to be relatively stable in DMF, we explored potential activation of NBS by the substrate itself through protonation. The ^{1}H NMR spectrum for 1*H*-indazole-3-carboxylic acid in DMF clearly showed each proton on the aromatic ring, as well as a broad singlet corresponding to a mixture of the carboxylic acid, indazole N–H, and traces of water. When the acid was combined with NBS, there was a clear chemical shift of the aliphatic protons of the NBS, as well as the appearance of a new aliphatic peak associated with the byproduct, succinimide. The observed chemical shift for NBS suggested that



Scheme 5 Possible mechanism through a radical pathway

the indazole interacts with NBS, most likely through the carboxylic acid O–H and the carbonyl groups of NBS.

With the ^{1}H NMR evidence suggesting that the substrate is involved in the activation of NBS towards dissociation, and the use of a radical quencher stopping the reaction, even in the apparent presence of bromine, we believe it is highly likely that the reaction proceeds by a radical pathway. Although not definitive, a possible mechanism is shown in Scheme 5. The reaction is initiated by protonation of NBS by the indazolecarboxylic acid, which helps to activate the N–Br bond towards homolytic cleavage to form bromine. The bromine then undergoes light-mediated and/or thermal homolytic cleavage to produce bromine radicals. A bromine radical abstracts the acidic proton of the indazolecarboxylic acid, and subsequent decarboxylation produces an indazole free radical that reacts with another equivalent of bromine to form the brominated product.

Having previously established that azahetarenecarboxylic acids undergo metal- and catalyst-free decarboxylative halogenation, we sought to investigate the mechanism by which the reaction occurs. Although we cannot completely rule out alternative mechanisms, our studies suggest that the reaction proceeds by a radical pathway. The yield of the reaction is higher when the chemistry is conducted in the presence of light, and the reaction fails to proceed in the presence of the radical quencher TEMPO. We believe that the acidic reaction environment influences the reactivity of NBS, and so catalyses the formation of bromine that subsequently reacts through a radical pathway to form the decarboxylative brominated product.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707901.

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(15) **Bromination of Azahetarenecarboxylic Acids; General Procedure**
The appropriate carboxylic acid (0.280 mmol) was dissolved in the solvent (1.5 mL) and NBS (0.280 mmol) was added. The vessel was sealed and the mixture was stirred at rt for 16 h. H_2O (10 mL) was added and the organic material was extracted with EtOAc (2 × 4 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography (silica gel, EtOAc–PE or CH_2Cl_2–MeOH).
(16) **3-Bromo-1H-indazole (Table 1, Entry 1)**
Colourless solid; yield: 36 mg (67%); mp 145–150 °C (Lit.[14] 142–143 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (br s, 1 H, NH), 7.58 (m, 2 H, ArH), 7.39 (m, 1 H, ArH), 7.17 (m, 1 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 128.3, 123.1, 122.6, 121.9, 120.2, 110.7. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_7H_6BrN_2$: 196.9709; found: 196.9717.
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■■Refs 15–21 renumbered in text order; confirm OK■■