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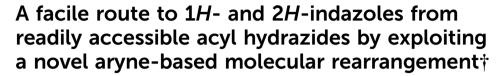


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Herein we report the transformation of readily synthesised acyl hydrazides into 2-hydrazobenzophenones *via* a novel molecular rearrangement pathway using aryne chemistry. The developed reaction protocol is performed under relatively mild conditions and is tolerant of a wide variety of functional groups, and the 2-hydrazobenzophenone products provide access to both 1*H*-and 2*H*-indazoles from a single intermediate.

The indazole moiety is of great medicinal importance¹ and compounds containing the indazole nucleus have recently sparked great interest for use as anti-inflammatory,² antitumour^{3,4} and anti-HIV⁵ agents, and as inhibitors of protein kinase, HIVprotease,⁷ monoamine oxidase⁸ and *N*-myristoyltransferase,⁹ as well as finding use as a biological probe, 10 amongst other applications. However, most strategies for the synthesis of indazoles are generally limited by their requirement of using complex multi-step syntheses, 11 and/or using harsh reaction conditions that often promote alternative reaction pathways (e.g. undesirable Wolff-Kishner reduction is often observed in hydrazine-based synthesis for the preparation of indazoles)¹² and/or poor functional group tolerance. 13 This highlights a general need for synthetic routes that facilitate the synthesis of indazoles, especially those that start from readily accessible starting materials.

Over the past few decades, owing in large part to the plethora of new methodologies that have enabled facile access to arynes, 14,15 the employment of aryne chemistry in synthesis has seen a major resurgence. A salient feature of aryne chemistry is the possibility for the formation of C–C and C–heteroatom bonds on aryl rings, resulting in the synthesis of various di- and even tri-substituted arenes (*i.e.* if the aryne was already substituted). Owing to this, aryne chemistry has

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emerged as a very useful method for the synthesis of benzo-fused heterocycles. 25 Of particular relevance to this article is the use of aryne chemistry to synthesise indazoles, i.e. through the use of N-tosylhydrazones²⁶ and *in situ* generation of nitrile imines²⁷ (for 1*H*-indazoles) or by using sydnones²⁸ (for 2*H*-indazoles). Whilst these methods have been successfully utilised to selectively afford 1H- or 2H-indazoles, the requirement of a phase transfer catalyst additive, limited scope (i.e. for the synthesis of 1,3-diarylindazoles only), and the reliance on the use of precursors that require lengthy/cumbersome syntheses (respectively), highlights several key limitations. Moreover, none of these syntheses provide flexible access to both 1H- and 2H-indazoles from a single branch point. As such, despite the inherently favourable nature of aryne chemistry to provide benzo-fused heterocycles, there is still significant scope for development in this area in terms of providing routes to indazoles. This is especially pertinent as currently there is no leading synthetic strategy to synthesise both 1H- and 2H-indazoles in a more general sense, i.e. outside the scope of aryne-based chemistry.

Recently our group^{29,30} and others^{31–34} have reported on acyl hydrazides as synthetically versatile scaffolds for the synthesis of a wide range of species. More specifically, acyl hydrazides have been employed in the creation of moieties such as amides, 35 esters, 35 thioesters, 35 ketones, 36 N-acyl carbamates 37 and 1,3,4-oxadiazoles,38 as well as being used as building blocks for the creation of bioactive molecules such as hydroxamic acids³⁹ and macrocyclic enamides.⁴⁰ Approaches to utilise acyl hydrazides in synthesis have largely focused on substituting the hydrazide moiety35,36,39 or alkylating at the relatively acidic N-H position (see Scheme 1). 37,40 In this work, it was envisioned that the reaction of an arvne with an acyl hydrazide would exploit both of these synthetic properties to facilitate a molecular rearrangement reaction pathway that would lead to the synthesis of 2-hydrazobenzophenones. These entities could then act as a single branch point for conversion into 1H- or 2H-indazoles by exploiting the removal of the carbamate groups pre- and post-alkylation (Scheme 1).

 $[\]dagger$ Electronic supplementary information (ESI) available: NMR (1H and ^{13}C), IR, LRMS (ESI) and HRMS (ESI) of all featured compounds. See DOI: 10.1039/c8cc06556j

Communication ChemComm

Scheme 1 General method for the synthesis of 2-hydrazobenzophenones from acyl hydrazides *via* benzyne chemistry and the proposed mechanism for use as a single branch point for the formation of 1*H*- and 2*H*-indazoles.

Our study began with the reaction of acyl hydrazide 1a with benzyne precursor 2 in the presence of a fluoride source tetrabutylammonium difluorotriphenylsilicate (TBAT), with the aim of forming 2-hydrazobenzophenone 3a via a novel molecular rearrangement pathway (see Scheme 4 below for the proposed mechanism). Initially, the reaction was carried out under the conditions developed by Pintori et al. for the aryl insertion of arynes into amide C(O)-N bonds, 41 i.e. the use of 1.5 equivalents of the benzyne precursor, 2 equivalents of TBAT and toluene as the reaction solvent at 50 °C. To our delight, the reaction proceeded efficiently, resulting in the formation of the desired product 3a in 86% yield (Table 1, entry 1). Lowering the equivalents of the fluoride source in the reaction resulted in incomplete conversion of acyl hydrazide 1a and thus had a negative impact on the yield (Table 1, entries 2 and 3). Whilst other carbamate groups could be used for this transformation (see the ESI† for details), i-Pr carbamates provided the highest yield.

With the optimised conditions for the transformation of acyl hydrazides into 2-hydrazobenzophenones in hand, we took the opportunity to investigate the applicability of our protocol for the formation of various 2-hydrazobenzophenones (Scheme 2). A range of acyl hydrazides were examined (1a–1l) under the developed reaction conditions. All the starting acyl hydrazides were prepared in good yields using our previously reported procedure for the hydroacylation of azodicarboxylates (see the ESI† for details). ^{29,30}

To our delight, the reaction of acyl hydrazides **1a–1l** with benzyne was tolerant of various functional groups on the aromatic acyl hydrazide motif, *e.g.* electron-withdrawing (halo, trifluoromethyl, ester, and nitro), electron-rich (methyl and methoxy) and electronneutral (hydrogen) functionalities (Scheme 2). Unfortunately, the presence of *ortho*-functional groups on the aryl ring resulted in a

Table 1 Reaction optimisation of acyl hydrazide and benzyne

Entry	2 (eq.)	TBAT (eq.)	Base/eq.	Conversion of 1a (%)	3a (%)
1	1.5	2	3	100	86
2	1.5	1.5	3	76	59
3	1.5	1	5	54	38

Reaction conditions: acyl hydrazide 1a (0.5 mmol, 1 eq.), benzyne precursor 2 (0.75 mmol, 1.5 eq.) and TBAT in toluene (6 mL); 50 $^{\circ}{\rm C}$ for 16 h.

Scheme 2 Scope of reaction with respect to acyl hydrazide **1**. Reaction conditions: acyl hydrazides **1a–1l** (0.5 mmol, 1 eq.), benzyne precursor **2** (0.75 mmol, 1.5 eq.) and TBAT (1 mmol, 2 eq.) in toluene (6 mL); 50 °C for 16 h.

lower yield of the desired products (3k and 3l). This is likely due to increased steric hindrance about the amide-like carbonyl promoting carbanionic attack on a carbamate carbonyl. This hypothesis is further substantiated by the *ortho*-fluoro variant (with fluoride being a steric isostere for H) affording product 3j in a higher yield, 70%.

To appraise the notion that the cleavage of the carbamate moieties in 2-hydrazobenzophenones would result in subsequent intramolecular dehydrative cyclisation to form desired 1*H*-indazoles, removal of the carbamates of compound 3a was attempted under a variety of conditions (see Table 2). The use of Lewis acid AlCl₃ resulted in incomplete conversion of the starting material 3a and only carbamate 1*H*-indazole 5 was observed in 30% yield (Table 2, entry 1). Refluxing in AcOH or HCl (3 M) resulted in complete conversion of the starting material and gave access to carbamate 1*H*-indazole 5 only, in 65% and 71% yields, respectively. Pleasingly, however, the use of either 12 M HCl or KOH in dimethylacetamide resulted in excellent yields, >90%, of the desired 1*H*-indazole 4a (Table 2, entries 4 and 5).

Having established suitable reaction conditions for the removal of the isopropyl carbamate groups and dehydrative cyclisation, the previously formed library of 2-hydrazobenzophenones 3a–3l were subjected to the relatively mild basic reaction conditions for the formation of various 1*H*-indazoles (Scheme 3). Most pleasingly,

Table 2 Reaction optimisation for the synthesis of 1H-indazole

Entry	Reagent	Solvent	Temperature (°C)	Yield 4a (%)	Yield 5 (%)
1	AlCl ₃	MeNO ₂	60	0	30^a
2	AcOH	_	Reflux	0	71
3	HCl (3 M)	_	Reflux	0	65
4	HCl (12 M)	_	Reflux	91	0
5	KOH _(aq)	DMA	60	92	0

Reaction conditions: 2-hydrazobenzophenone 3a (0.5 mmol) under varying conditions for 16 h. DMA = dimethylacetamide. a 45% conversion of 3a.

ChemComm Communication

Scheme 3 Scope of reaction with respect to acyl hydrazide 3. Reaction conditions: 2-hydrazobenzophenones 3a-3l (0.25 mmol, 1 eq.) and KOH (1.00 mmol, 4 eq. in H₂O (3 mL)) in DMA (5 mL); 60 °C for 16 h. ^a Reaction was carried out at 100 °C. ^bUsing 3e as acyl hydrazide. ^cHCl (12 M) conditions.

excellent yields were observed across the series with the exception of the 2-hydrazobenzophenone containing the nitro functionality. Fortunately, and highlighting the advantage of being able to employ either basic of acidic conditions, subjecting nitro 2-hydrazobenzophenone 3i to the developed acidic reaction conditions resulted in a high yield, 79%. We also note that 1*H*-indazoles can be readily and selectively 1*H*-alkylated using one of several reported procedures. 42-44

Compared to 1*H*-indazoles, 2*H*-indazoles have historically been more challenging to prepare. As a result, 2*H*-indazoles have been far less studied. From the outset, we wanted to establish a method in which the synthesis of *N*-substituted 2*H*-indazoles could be enabled from a common intermediate to that used in the synthesis of the 1*H*-indazoles. We postulated that alkylation of 2-hydrazobenzophenones prior to carbamate removal (and subsequent dehydrative cyclisation) would result in the selective formation of *N*-substituted 2*H*-indazoles. To appraise this, alkylation of 2-hydrazobenzophenone 3a was carried out to form alkylated 2-hydrazobenzophenone 6. Compound 6 was then subjected to the various deprotection conditions (see Table 3) to try and form *N*-methylated 2*H*-indazole 7a. Fortunately, refluxing HCl (12 M) resulted in

 Table 3
 Reaction optimisation for the formation of 2H-indazole

Entry	R	Reagent	Solvent	Temperature (°C)	Yield 7a (%)	Yield 8 (%)
1	Ме	AcOH	_	Reflux	0	70
2	Me	HCl (12 M)	_	Reflux	91	0
3	Me	KOH _(aq)	DMA	60	0	84

Reaction conditions: alkylated 2-hydrazobenzophenone 6 (0.5 mmol) under varying conditions for 16 h. DMA = dimethylacetamide.

the formation of the desired *N*-methyl 2*H*-indazole. The use of refluxing AcOH or aqueous KOH in dimethylacetamide only resulted in the cleavage of the internal carbamate, forming the undesired product **8**; although we do note that this product was formed selectively and in good yield. Having successfully formed 2*H*-indazole 7a *via* alkylation and subsequent removal of carbamates, the reaction sequence was then applied successfully for the formation of functional 2*H*-indazole 7b (Table 3, inset) in 79% yield from 2-hydrazobenzophenone 3a over 2 steps.

We next chose to probe the mechanism for the reaction of acyl hydrazide and benzyne. It was important to note, as the starting point, that acyl hydrazides have previously been shown to act as acyl halide analogues,35 and acyl halides and amides have been shown to react with benzynes via an aryl insertion mechanism where the aryne is inserted into the C-halogen σ-bond. 41,46 Therefore, arvne insertion into the C(O)-α-nitrogen bond was considered as a plausible mechanistic pathway (Scheme 4, path A). Alternatively, we needed to consider that acyl hydrazides can react nucleophilically at the β-nitrogen atom and that this position may or may not be deprotonated under the reaction conditions (Scheme 4, paths B and C). Therefore, it was necessary to establish whether arynes insert into the C-N σ-bond in acyl hydrazides (Scheme 4, path A) or whether they undergo a novel molecular rearrangement following nucleophilic attack from the more nucleophilic nitrogen atom (Scheme 4, paths B and C).

To appraise the feasibility of the reaction pathways, methylated acyl hydrazide 9 was synthesised and subjected to the aryne functionalisation reaction conditions (Scheme 5). Under the reaction conditions, no reaction between the methylated acyl hydrazide 9 and benzyne was observed. If the reaction pathway proceeded via path A, then it would have been expected that the methylated-hydrazobenzophenone product 6 would have formed under these conditions. The almost quantitative recovery of the starting material suggested that the presence of the N-H bond in the starting material is important for the reaction to proceed. Therefore, we next evaluated whether the acyl hydrazide was deprotonated under the reaction conditions, owing to the acidity of the N-H bond. To do this, acyl hydrazide 1a was reacted with 1.1 eq. of iodomethane in the presence of 1.1 eq. of TBAT in toluene at 50 °C (Scheme 5). A control experiment in the absence of TBAT was conducted in parallel. It was observed that in the

Scheme 4 Possible reaction mechanisms.

Communication ChemComm

Scheme 5 Mechanistic studies

presence of TBAT, a significant amount of methylated acyl hydrazide 9, 90%, was observed (Scheme 5). In the absence of TBAT, a near quantitative amount of the starting material was recovered. We therefore felt that it was appropriate to conclude that an acyl hydrazide would be significantly deprotonated under the reaction conditions, and suggest that the reaction proceeds through the novel molecular reaction pathway C (Scheme 4).

In conclusion, we have exploited a novel molecular rearrangement pathway involving the reaction of readily accessible acyl hydrazides with arynes to provide an intermediate that can be readily converted into either a 1H- or a 2H-indazole, as desired. The developed reaction conditions enable their synthesis from a single intermediate branch point (i.e. providing a highly diverse synthetic route), unveil a novel molecular rearrangement pathway, and tolerate a range of functional groups, and the 1H-indazoles can be formed under either basic or acidic conditions (i.e. a highly flexible route). In view of this, we believe that the protocols which we hereby report for the facile synthesis of 1H- and 2H-indazoles from acyl hydrazides will have wide ranging applications, especially as indazoles are applied in a broad range of medicinal/biological applications. Moreover, the novel reaction pathway we disclose may lead to further exploitation of, or inspiration in, aryne-based molecular rearrangements.

Conflicts of interest

There are no conflicts to declare.

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