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A facile route to 1*H*- and 2*H*-indazoles from readily accessible acyl hydrazides by exploiting a novel aryne-based molecular rearrangement†

André Shamsabadi and Vijay Chudasama *

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,⁶ HIV-protease,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.^{16–21} 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).^{22–24} Owing to this, aryne chemistry has

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 1*H*- or 2*H*-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 1*H*- and 2*H*-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 1*H*- and 2*H*-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 carbamates³⁷ 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 moiety^{35,36,39} 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 aryne 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 1*H*- or 2*H*-indazoles by exploiting the removal of the carbamate groups pre- and post-alkylation (Scheme 1).

Department of Chemistry, University College London, London, UK.

E-mail: v.chudasama@ucl.ac.uk

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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 1H- and 2H-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 electron-neutral (hydrogen) functionalities (Scheme 2). Unfortunately, the presence of *ortho*-functional groups on the aryl ring resulted in a

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 1H-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 1H-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 1H-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 1H-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 1H-indazoles (Scheme 3). Most pleasingly,

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 °C for 16 h.

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**.

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. ^aReaction 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 or 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.⁴⁵ 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 2*H*-indazole

Entry	R	Reagent	Solvent	Temperature (°C)	Yield 7a (%)	Yield 8 (%)
1	Me	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 benzyne *via* an aryl insertion mechanism where the aryne is inserted into the C-halogen σ-bond.^{41,46} Therefore, aryne 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.

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 *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.

Notes and references

- 1 I. Denya, S. F. Malan and J. Joubert, *Expert Opin. Ther. Pat.*, 2018, **28**, 441–453; S. El Kazzouli and G. Guillaumet, *Tetrahedron*, 2016, **72**, 6711–6727; N. A. S. Ali, B. A. Dar, V. Pradhan and M. Farooqui, *Mini-Rev. Med. Chem.*, 2013, **13**, 1792–1800; D. D. Gaikwad, A. D. Chapolikar, C. G. Devkate, K. D. Warad, A. P. Tayade, R. P. Pawar and A. J. Domb, *Eur. J. Med. Chem.*, 2015, **90**, 707–731.
- 2 A. Guglielmotti, A. C. de Joannon, N. Cazzolla, M. Marchetti, L. Soldo, G. Cavallo and M. Pinza, *Pharmacol. Res.*, 1995, **32**, 369–373.
- 3 M. J. Clarke, *Coord. Chem. Rev.*, 2003, **236**, 209–233.
- 4 A. Shrivastava, A. K. Chakraborty, N. Upmanyu and A. Singh, *Austin J. Anal. Pharm. Chem.*, 2016, **3**, 1–23.
- 5 J.-H. Sun, C. A. Teleha, J.-S. Yan, J. D. Rodgers and D. A. Nugiel, *J. Org. Chem.*, 1997, **62**, 5627–5629.
- 6 K. W. Woods, *et al.*, *Bioorg. Med. Chem.*, 2006, **14**, 6832–6846.
- 7 M. Patel, J. D. Rodgers, R. J. McHugh, B. L. Johnson, B. C. Cordova, R. M. Klabbe, L. T. Bacheler, S. Erickson-Viitanen and S. S. Ko, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3217–3220.
- 8 N. T. Tzvetkov, S. Hinz, P. Küppers, M. Gastreich and C. E. Müller, *J. Med. Chem.*, 2014, **57**, 6679–6703.
- 9 A. Mousnier, *et al.*, *Nat. Chem.*, 2018, **10**, 599–606.
- 10 E. Robinson, E. Knight, N. Smoktunowicz, R. C. Chambers, G. G. Inglis, V. Chudasama and S. Caddick, *Org. Biomol. Chem.*, 2016, **14**, 3198–3201.
- 11 X. Xiong, Y. Jiang and D. Ma, *Org. Lett.*, 2012, **14**, 2552–2555.
- 12 K. Lukin, M. C. Hsu, D. Fernando and M. R. Leanna, *J. Org. Chem.*, 2006, **71**, 8166–8172.
- 13 C. S. Cho, D. K. Lim, N. H. Heo, T.-J. Kim and S. C. Shim, *Chem. Commun.*, 2004, 104–105.
- 14 Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, 1211–1214.
- 15 F. I. M. Idris and C. R. Jones, *Org. Biomol. Chem.*, 2017, **15**, 9044–9056.
- 16 P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550–3577.
- 17 J. Shi, Y. Li and Y. Li, *Chem. Soc. Rev.*, 2017, **46**, 1707–1719.
- 18 R. W. Hoffmann and K. Suzuki, *Angew. Chem., Int. Ed.*, 2013, **52**, 2655–2656.
- 19 J.-A. García-López and M. F. Greaney, *Chem. Soc. Rev.*, 2016, **45**, 6766–6798.
- 20 S. S. Bhojgude, A. Bhunia and A. T. Biju, *Acc. Chem. Res.*, 2016, **49**, 1658–1670.
- 21 C. Holden and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2014, **53**, 5746–5749.
- 22 F. I. M. Idris, C. E. Majesté, G. B. Craven and C. R. Jones, *Chem. Sci.*, 2018, **9**, 2873–2878.
- 23 L.-N. Guo, H. Wang and X.-H. Duan, *Org. Biomol. Chem.*, 2016, **14**, 7380–7391.
- 24 J. Shi, D. Qiu, J. Wang, H. Xu and Y. Li, *J. Am. Chem. Soc.*, 2015, **137**, 5670–5673.
- 25 A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191–218.
- 26 P. Li, J. Zhao, C. Wu, R. C. Larock and F. Shi, *Org. Lett.*, 2011, **13**, 3340–3343.
- 27 C. Spiteri, S. Keeling and J. E. Moses, *Org. Lett.*, 2010, **12**, 3368–3371.
- 28 P.-F. Wang, Y.-S. Feng, Z.-F. Cheng, Q.-M. Wu, G.-Y. Wang, L.-L. Liu, J.-J. Dai, J. Xu and H.-J. Xu, *J. Org. Chem.*, 2015, **80**, 9314–9320.
- 29 V. Chudasama, J. M. Ahern, D. V. Dhokia, R. J. Fitzmaurice and S. Caddick, *Chem. Commun.*, 2011, **47**, 3269–3271.
- 30 V. Chudasama, A. R. Akhbar, K. A. Bahou, R. J. Fitzmaurice and S. Caddick, *Org. Biomol. Chem.*, 2013, **11**, 7301–7317.
- 31 G. N. Papadopoulos, D. Limnios and C. G. Kokotos, *Chem. – Eur. J.*, 2014, **20**, 13811–13814.
- 32 I. Ryu, A. Tani, T. Fukuyama, D. Ravelli, S. Montanaro and M. Fagnoni, *Org. Lett.*, 2013, **15**, 2554–2557.
- 33 A. Mariappan, K. Rajaguru, S. Muthusubramanian and N. Bhuvanesh, *Tetrahedron Lett.*, 2015, **56**, 338–341.
- 34 A. Shamsabadi and V. Chudasama, *Org. Biomol. Chem.*, 2017, **15**, 17–33.
- 35 A. Maruani, M. T. W. Lee, G. Watkins, A. R. Akhbar, H. Baggs, A. Shamsabadi, D. A. Richards and V. Chudasama, *RSC Adv.*, 2016, **6**, 3372–3376.
- 36 A. R. Akhbar, V. Chudasama, R. J. Fitzmaurice, L. Powell and S. Caddick, *Chem. Commun.*, 2014, **50**, 743–746.
- 37 A. Shamsabadi, J. Ren and V. Chudasama, *RSC Adv.*, 2017, **7**, 27608–27611.
- 38 O. Sugimoto, T. Arakaki, H. Kamio and K. Tanji, *Chem. Commun.*, 2014, **50**, 7314.
- 39 G. N. Papadopoulos and C. G. Kokotos, *Chem. – Eur. J.*, 2016, **22**, 6964–6967.
- 40 Y. J. Kim and D. Lee, *Org. Lett.*, 2004, **6**, 4351–4353.
- 41 D. G. Pintori and M. F. Greaney, *Org. Lett.*, 2010, **12**, 168–171.
- 42 D. J. Slade, N. F. Pelz, W. Bodnar, J. W. Lampe and P. S. Watson, *J. Org. Chem.*, 2009, **74**, 6331–6334.
- 43 A. Schmidt, A. Beutler and B. Snovydyovych, *Eur. J. Inorg. Chem.*, 2008, 4073–4095.
- 44 M.-H. Lin, H.-J. Liu, W.-C. Lin, C.-K. Kuo and T.-H. Chuang, *Org. Biomol. Chem.*, 2015, **13**, 11376–11381.
- 45 N. Cankařová, J. Hlaváč and V. Křehňák, *Org. Prep. Proced. Int.*, 2010, **42**, 433–465.
- 46 H. Yoshida, Y. Mimura, J. Ohshita and A. Kunai, *Chem. Commun.*, 2007, 2405–2407.