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Synthesis of spiro-3*H*-indazoles via 1,3-dipolar cycloaddition of arynes with 6-diazocyclohex-2-en-1-one derivatives and fused-2*H*-indazoles by subsequent rearrangement†

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A route to rare spiro-3*H*-indazoles bearing a carbonyl group adjacent to the spirocyclic quaternary carbon via 1,3-dipolar cycloaddition reaction of arynes with 6-diazocyclohex-2-en-1-one derivatives under mild conditions has been developed. Further transformation of these unique spiro-3*H*-indazoles via an acid- or heat-mediated rearrangement to fused-2*H*-indazoles and an interesting reduction/ring-opening/reduction sequence are also described.

Introduction

Since *o*-(trimethylsilyl)aryl triflate was introduced as a new aryne precursor,¹ aryne chemistry has enjoyed impressive advances over the last decades.² Among them, the 1,3-dipolar cycloaddition reaction of arynes with dipoles as an efficient synthetic method to construct heterocycles has been extensively studied. However, to use diazo compounds as the dipoles, these accomplishments mainly dealt with open-chain diazo substrates,^{3,4} and there were seldom reports involving cyclic diazo compounds.⁵ It is well-known that ordinary small molecule diazo compounds, like diazomethane, are highly unstable, dangerous and potentially explosive. Thus, an electron-withdrawing group (*e.g.*, carbonyl group) conjugated to the diazo functional group is usually introduced to make them relatively stable. However, using this type of diazo substrate to construct spiroindazoles would lead to a carbonyl group adjacent to the spirocyclic quaternary carbon, a skeleton liable to undergo rearrangement *via* acyl migration.^{4,6,7} Thus, this is sometimes a dilemma. To address this issue, Shi⁸ and Moses⁹ adopted safe surrogates of diazo compounds, *e.g.*, *N*-tosylhydrazide and hydrazonyl chloride, to synthesize indazoles *via*

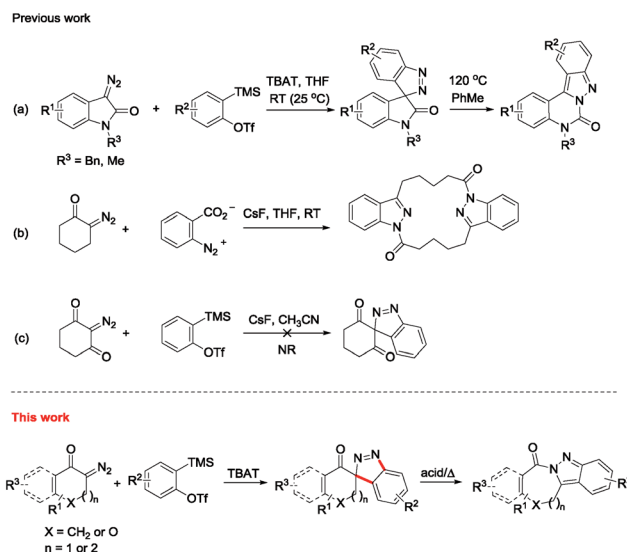
dipolar cycloaddition, but their methods were only applied to the synthesis of non-spiroindazoles. Recently, we disclosed the first isolated spiro[indazole-3,3'-indolin]-2'-ones *via* 1,3-dipolar cycloaddition reaction from arynes and 3-diazoindolin-2-ones (Scheme 1, eqn (a)).¹⁰ We wondered whether ordinary cyclic diazo compounds could also realize the similar transformation to afford spiroindazole through slightly tuning substrate structure. In this regard, there was only one successful spiroindazole example documented in literature⁶ besides our previous report, although great efforts had been devoted to tackle this issue. For example, Shechter explored the reaction of

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Scheme 1 Synthetic route to spiro-3*H*-indazoles and fused-2*H*-indazoles.



diazo cyclohexone with diazotized anthranilic acid, and a dimer was obtained as the major product in low yield (eqn (b)).⁶ Larock's group tried in vain to prepare a spiroindazole from 2-diazocyclohexane-1,3-dione, as there was no reaction detected in their system (eqn (c)).⁴ Given impressive bioactivities and medicinal applications of indazoles, such as anti-inflammatory, anti-tumor, and anti-HIV activity, among others,¹¹ we embarked on extensive studies of the synthesis of spiroindazoles through 1,3-dipolar cycloaddition of ordinary cyclic diazo compounds and arynes.

Results and discussion

We first investigated the reaction of literature substrates **1a** and **1b** with *o*-(trimethylsilyl)phenyl triflate (**2a**) under our previous optimal conditions (Table 1, entries 1 and 2).¹⁰ There was no reaction for substrate **1a**, probably due to the low reactivity of the diazo group between the two carbonyl groups, while a complex reaction mixture was formed for substrate **1b**. Then we turned our attention to substrates **1c–e**. Using **1c** as the diazo substrate, again only a complex reaction system was obtained (entry 3). Delightedly, we isolated the desired product **3d** in 91% yield, when **1d** was employed (entry 4). Of note, this result was different from that of structural analogue **1c**. After these initial trials we intended to modify the reaction conditions with diazo substrate **1d** and aryne precursor **2a** (entries 5–9). Increase of the loading of **2a** from 1.2 equiv. to 1.5 equiv. slightly enhanced the yield of **3a** to 93% (entry 5). Changing the fluoride source and solvent did not give any better results (entries 6–9). Oddly there was no reaction at all with the combination of CsF/THF

(entry 8). In view of the substrates (**1a–d**) and respective results, the substrate **1e** was also examined under the reaction conditions. To our delight, it worked smoothly as well to afford the spiroindazole **3e** in 79% yield.

With the reaction conditions optimized, the scope of the 1,3-dipolar cycloaddition reaction was explored. As illustrated in Table 2, we first tested the derivatives of **1d**. For F, Br and MeO

Table 2 Scope of diazo compounds and arynes^a


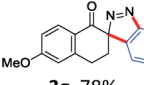
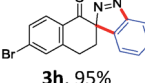
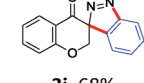

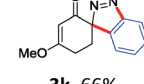
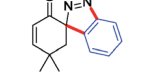
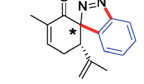
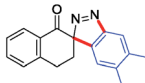
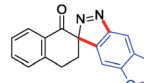
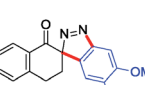
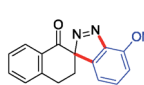
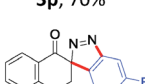
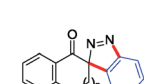

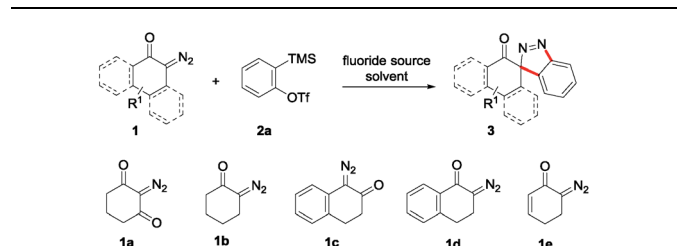
Entry	Product ^b (yield)	Entry	Product ^b (yield)
1	 3f , 80%	2	 3g , 78%
3	 3h , 95%	4	 3i , 68%
5	 3j , 87%	6	 3k , 66%
7	 3l , 88%	8	 3m , 81%
9	 3n , 86%	10	 3o , 80%
11	 3p , 70%	12	 3q , 92%
13	 3r ^c	14	 3s ^c
15	 3t ^d		

Table 1 Optimization of reaction conditions^a



Entry	Diazo compound	Fluoride source	Solvent	Yield ^b (%)
1	1a	TBAT	THF	NR
2	1b	TBAT	THF	^e
3	1c	TBAT	THF	^e
4	1d	TBAT	THF	91
5 ^c	1d	TBAT	THF	93
6 ^{c,d}	1d	KF	THF	78
7 ^c	1d	TBAF	THF	79
8 ^c	1d	CsF	THF	NR
9 ^c	1d	CsF	CH ₃ CN	87
10 ^c	1e	TBAT	THF	79

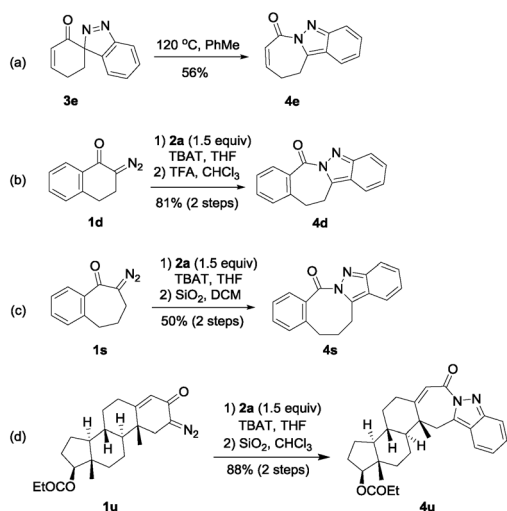
^a Conditions: **1** (0.3 mmol), **2a** (1.2 equiv.), fluoride source (1.5 equiv.), solvent (3 mL), 0 to 20 °C, air. ^b Isolated yields. ^c **2a** (1.5 equiv.) was employed instead. ^d 18-crown-6 was added as the additive. ^e Complex system was got. TBAT = tetrabutylammonium triphenyldifluorosilicate.

^a Conditions: **1** (0.3 mmol), **2** (0.45 mmol, 1.5 equiv.), TBAT (0.45 mmol, 1.5 equiv.), solvent (3 mL), 0 to 20 °C, air. ^b Isolated yields. ^c Pure sample could not be obtained. ^d No desired product was formed. ^e The ratio was determined by the quantity of isolated product.

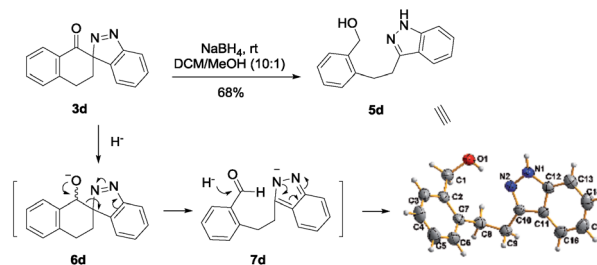


substituted substrates (**1f–h**), all of them reacted well to afford the corresponding spiroindazoles (**3f–h**) in 78–95% yields. 3-Diazochroman-4-one was also a suitable substrate and the desired product **3i** was obtained in 68% yield. Then we investigated a series of substituted 6-diazocyclohex-2-en-1-one derivatives (**1j–m**). The reaction of both mono-substituted and di-substituted diazocyclohex-2-en-1-ones proceeded smoothly to deliver the desired spiroindazoles in moderate to good yields. It's interesting to note that for **1m**, an *i*-propenyl group adjacent to the diazo moiety did not have adverse effect on the yield. The performance of substituted aryne precursors was also examined. Symmetrical aryne precursors (**2b–d**) gave the desired spiro products (**3n–p**) in satisfactory yields and unsymmetrical 3-methoxybenzyne furnished a single isomer **3q** in 92% yield.^{3b,4,12} The spiroindazoles **3r** and **3s** were determined just by their crude ¹H and ¹³C-NMR spectra due to their lability resulting from high propensity towards isomerization to afford fused-indazoles (for the same transformation see Scheme 2). Unexpectedly, 2-diazo-2,3-dihydro-1*H*-inden-1-one gave a complex mixture instead of the desired product **3t**. We speculated that it may be due to the presence of acidic proton at the benzyl position and also the adjacent position of diazo group.

Migration of acyl, alkyl or aryl group of 3*H*-pyrazoles leading to 1*H*-pyrazoles has been well documented,¹³ and a similar rearrangement of spiro[indazole-3,3'-indolin]-2'-ones was also observed in our study.¹⁰ As a synthetic application of these spiro-3*H*-indazoles, we allowed **3e** to be heated in PhMe at 120 °C, and the migration product **4e** was isolated in 56% yield (Scheme 2, eqn (a)). We also found that TFA and even weakly acidic CHCl₃ or SiO₂ could promote isomerization of these spiro-3*H*-indazoles (Scheme 2, eqn (b) and (c)). For example, **4d** and **4s** could be obtained in satisfying yields with TFA/CHCl₃ and SiO₂ to promote isomerization respectively. With these satisfying results, we intended to synthesize a range of fused indazoles from spiroindazoles (**3f–r**) generated from 1,3-dipolar cycloaddition reaction. However, we observed that this kind of isomerization promoted by heat or acids was only applicable to



Scheme 2 Synthesis of fused-2*H*-indazoles.



Scheme 3 Unexpected transformation of spiro-3*H*-indazole **3d**.

a limited amount of spiroindazoles, because side-reactions such as ring-opening or polymerization sometimes took place, resulting in the difficulty in isolating pure samples.⁶ To further demonstrate the advantages of this method to introduce fused indazole motif under mild conditions, we applied it to the derivation reaction of biomolecule testosterone propionate (Scheme 2, eqn (d)). Fused indazole **4u** could be readily prepared in 88% yield *via* a two-step manipulation.

On the other hand, we envisaged that if ketone **3d** was reduced to alcohol followed by being treated with acid and heating, it might undergo carbon cationic rearrangement to afford other fused heterocycles, for example cinnoline derivative. Unexpectedly, **5d** was isolated as the major product in 68% yield under the reduction conditions and its exact structure was further confirmed by X-ray diffraction studies (Scheme 3).¹⁴ The formation of **5d** could be rationalized by a sequence of reduction, ring-opening and a second reduction of the resulting aldehyde **7d**.

Conclusions

In summary, we have demonstrated an efficient synthesis of spiro-3*H*-indazoles *via* 1,3-dipolar cycloaddition of arynes with 6-diazocyclohex-2-en-1-one derivatives under mild conditions in good to excellent yields. These unique spiro-3*H*-indazoles could be further transformed to fused-2*H*-indazoles *via* acid- or heat-mediated rearrangement. For spiroindazole **3d**, an interesting sequential transformation involving reduction/ring-opening/reduction has been reported.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- 1 Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, 1211.
- 2 For reviews, see: (a) S. A. Worlikar and R. C. Larock, *Curr. Org. Chem.*, 2011, **15**, 3214; (b) S. S. Bhojgude and A. T. Biju, *Angew. Chem., Int. Ed.*, 2012, **51**, 1520; (c) A. Bhunia, S. R. Yetra and A. T. Biju, *Chem. Soc. Rev.*, 2012, **41**, 3140; (d) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191; (e) C. M. Gampe and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 3766; (f) R. Sanz, *Org. Prep. Proced. Int.*, 2008, **40**, 215; (g) H. Pellissier and M. Santelli, *Tetrahedron*, 2003, **59**, 701; (h) S. S. Bhojgude, A. Bhunia and A. T. Biju, *Acc. Chem. Res.*, 2016, **49**, 1658.
- 3 (a) For seminal work using diazo compounds and benzyne to construct indazoles, see: R. Huisgen and R. Knorr, *Naturwissenschaften*, 1961, **48**, 716; (b) T. Jin and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2007, **46**, 3323; (c) Y. Hari, R. Sone and T. Aoyama, *Org. Biomol. Chem.*, 2009, **7**, 2804.
- 4 Z. Liu, F. Shi, P. D. G. Martinez, C. Raminelli and R. C. Larock, *J. Org. Chem.*, 2008, **73**, 219.
- 5 (a) K. Hirakawa, T. Toki, K. Yamazaki and S. Nakazawa, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1944; (b) K. Hirakawa, Y. Minami and S. Hayashi, *J. Chem. Soc., Perkin Trans. 1*, 1982, 577; (c) W. Burgert, M. Große and D. Rewicki, *Chem. Ber.*, 1982, **115**, 309; (d) G. Baum, R. Bernard and H. Shechter, *J. Am. Chem. Soc.*, 1967, **89**, 5307.
- 6 T. Yamazaki and H. Shechter, *Tetrahedron Lett.*, 1973, **14**, 1417.
- 7 T. Yamazaki and H. Shechter, *Tetrahedron Lett.*, 1972, **13**, 4533.
- 8 P. Li, J. Zhao, C. Wu, R. C. Larock and F. Shi, *Org. Lett.*, 2011, **13**, 3340.
- 9 C. Spiteri, S. Keeling and J. E. Moses, *Org. Lett.*, 2010, **12**, 3368.
- 10 B. Cheng, B. Zu, B. Bao, Y. Li, R. Wang and H. Zhai, *J. Org. Chem.*, 2017, **82**, 8228.
- 11 For reviews, see: (a) S. Bräse, C. Gil and K. Knepper, *Bioorg. Med. Chem.*, 2002, **10**, 2415; (b) H. Cerecetto, A. Gerpe, M. González, V. J. Arán and C. O. de Ocariz, *Mini-Rev. Med. Chem.*, 2005, **5**, 869; (c) A. Schmidt, A. Beutler and B. Snovydyovych, *Eur. J. Org. Chem.*, 2008, 4073.
- 12 The regioselectivity of **3q** was assigned according to the analogous reaction of 3-methoxybenzyne with diazo compounds. For theoretical studies of the regioselectivities of aryne reactions, see: (a) P. M. Tadross, C. D. Gilmore, P. Bugga, S. C. Virgil and B. M. Stoltz, *Org. Lett.*, 2010, **12**, 1224; (b) J. M. Medina, J. L. Mackey, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 15798; (c) P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G.-Y. J. Im, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc.*, 2010, **132**, 1267.
- 13 For reviews, see: (a) M. P. Sammes and A. R. Katritzky, *Adv. Heterocycl. Chem.*, 1983, **34**, 1; (b) T. Nagai and M. Hamaguchi, *Org. Prep. Proced. Int.*, 1993, **25**, 403; for two recent examples, see: (c) M. C. Pérez-Aguilar and C. Valdés, *Angew. Chem., Int. Ed.*, 2013, **52**, 7219; (d) D. Gladow, S. Doniz-Kettenmann and H. Reissig, *Helv. Chim. Acta*, 2014, **97**, 808.
- 14 CCDC 1577009 (**5d**) contains the ESI crystallographic data.†

