ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2018, **54**, 13260

Received 13th September 2018,
Accepted 5th November 2018

DOI: 10.1039/c8cc07451h

rsc.li/chemcomm

Nitrostyrenes as 1,4-*CCNO*-dipoles: diastereoselective formal [4+1] cycloaddition of indoles†

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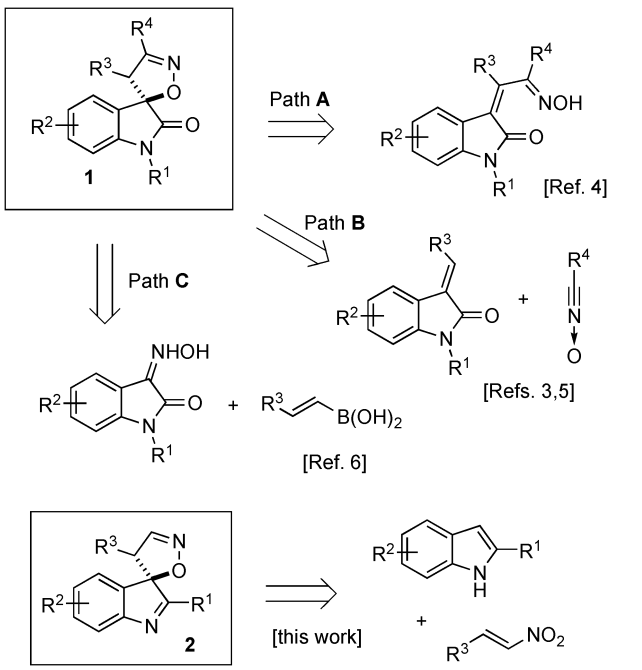
An unusual reactivity of nitrostyrenes in phosphorous acid was discovered, which permits the employment of these readily available synthons as 1,4-*CCNO*-dipole surrogates in a highly diastereoselective (4+1)-cycloaddition of indoles to afford 4′*H*-spiro[indole-3,5′-isoxazoles] in a diastereomerically pure form.

Although heterocyclic compounds with 4′*H*-spiro[indoline-3,5′-isoxazole] and 4′*H*-spiro[indole-3,5′-isoxazole] cores do not occur in nature, these synthetic drug-like molecules demonstrated promising antimicrobial, antifungal, and anticancer activities.[1,2] They were also employed as advanced intermediates in total syntheses of natural pyrrolidinoindoline alkaloids and their analogs.[3] Unsurprisingly, preparation of these structures became the focus of attention for many research groups around the world. Typically, such spiro-heterocyclic scaffold can be accessed *via* acid-assisted 1,5-spiro-cyclization of mono-oximes of 3-ene-2,5-diones (Scheme 1, Path A),[4] [3+2]-cycloaddition of nitrile-oxides to 3-methylene-oxindoles (Path B),[3,5] or metal-catalyzed selective vinylation of isatine-oximes with vinyl-boronic acids (Path C).[6] It should be pointed out that all these methods were demonstrated employing isatines, providing various derivatives of 4′*H*-spiro[indoline-3,5′-isoxazol]-2-one (**1**). However, to the best of our knowledge, currently there are no methods of accessing closely related spirocyclic scaffold **2**, bearing a carbon-based substituent (alkyl, aryl or hetaryl) at the C-2 of indole moiety. Herein, we wish to report an efficient and highly diastereoselective route towards 4′*H*-spiro[indole-3,5′-isoxazoles] (**2**) proceeding *via* unusual formal [4+1] cycloaddition reaction involving nitroalkene as 1,4-*CCNO*-dipole and nucleophilic C-3 of indole as the dipolarophilic C_1-moiety.



Scheme 1 Synthetic approaches to spirocyclic indolines.

Our group has had a long-standing interest in the development of Brønsted acid-assisted cascade heterocyclizations of nitro-compounds.[7,8] While studying the conjugate addition of indoles to nitroolefins (Scheme 2, Path D), we observed an unusual reactivity when the reaction was performed in polyphosphoric acid (PPA). Careful optimization of the reaction conditions allowed for achieving selective rearrangement of the nitro group into hydroxamic acid **6** (Path E).[9] The former underwent an unusual ANRORC[10] cascade at higher temperatures affording 2-quinolones **7** (Path F).[7] While experimenting with PPA, we came across a poor quality batch of P_2O_5 containing notable amounts of red phosphorus (arising from incomplete combustion during reagent manufacturing). Polyphosphoric acid prepared from this material had a distinct pink color, and the reaction between nitrostyrene

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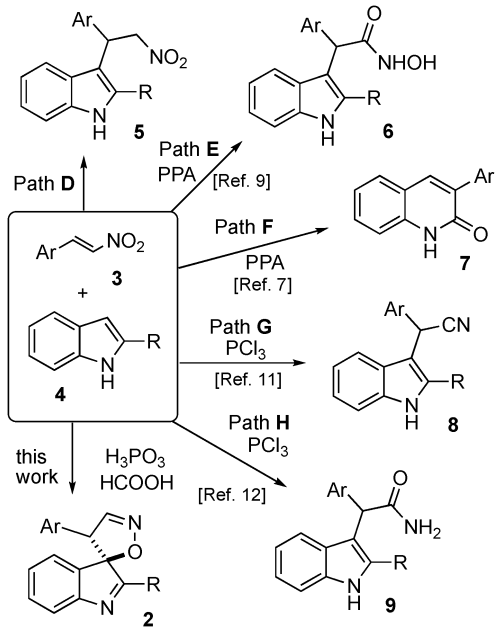
† Electronic supplementary information (ESI) available: Experimental details, spectral, crystallographic, and computational information (PDF). CCDC 1834625. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc07451h



Scheme 2 Diversity of products obtained upon alkylation of nitrostyrenes with indoles.

(**3a**, Ar = Ph) and 2-phenylindole (**4a**, R = Ph) carried out at room temperature in this medium led to the formation of notable amounts of unexpected spirocyclic structure **2aa** (R = Ar = Ph) alongside 2-quinolone **7** (Scheme 2) and other minor unidentified products. The molecular structure of **2aa** was unambiguously confirmed by single crystal X-ray crystallography (Fig. 1). Remarkably, this product was formed with perfect (3*R**,4′*S**)-diastereoselectivity, as shown. This finding justified further efforts towards the optimization of the reaction conditions for the selective synthesis of 3-indolinones **2**. We believed that the presence of low valent phosphorus additives must have caused this side reaction, so we continued to explore phosphorus(III) additives. Attempts to substitute PPA with PCl_3 resulted in *in situ* conversion of the nitro-group into a nitrile **8** (Path G)[11] or a carboxamide **9** (Path H).[12] We further tested the reaction in the presence of 2 equiv. of phosphorous acid in various organic media. It was found that **2aa** could be obtained in good yield if

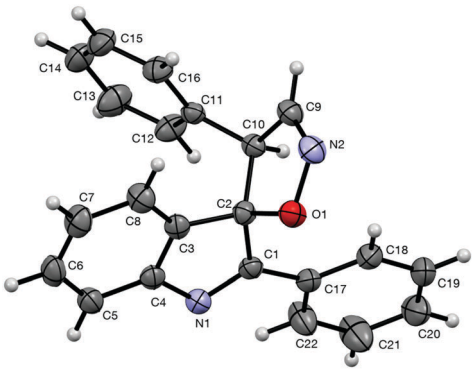
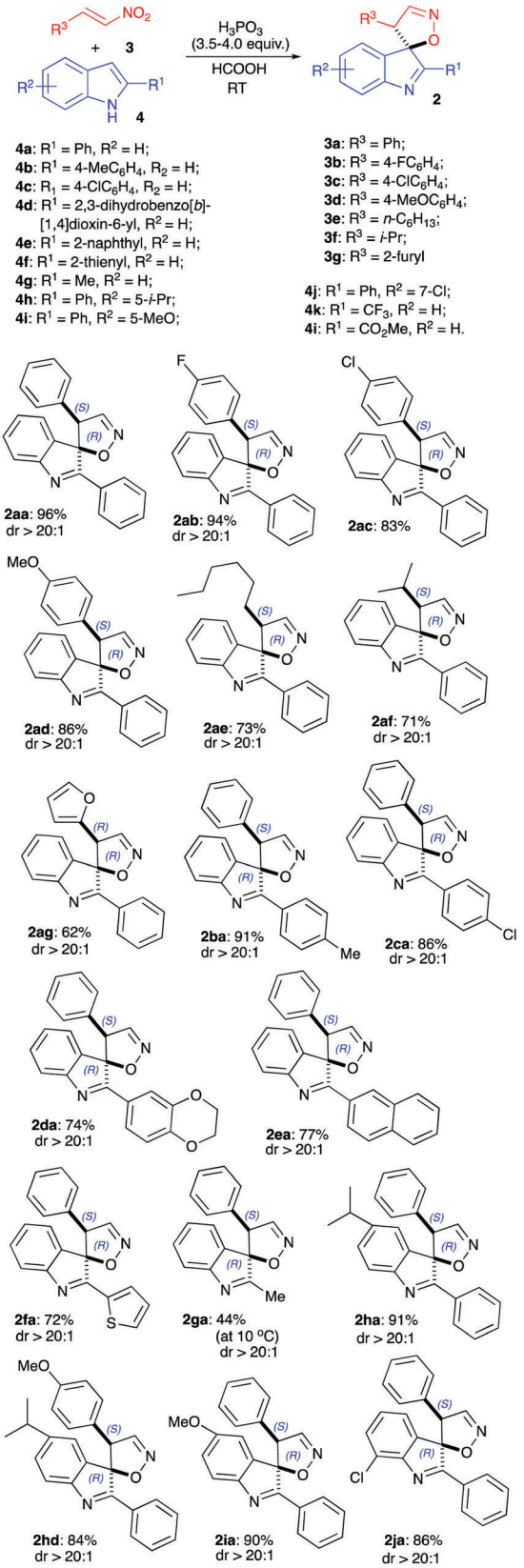
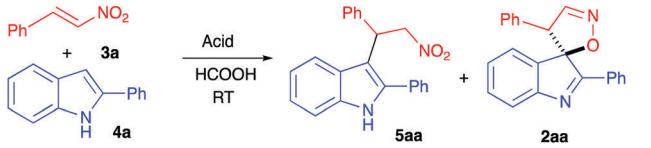


Fig. 1 ORTEP drawings of **2aa** (CCDC #1834625†) showing atom numbering schemes and 50% probability ellipsoids.



Scheme 3 Spirocycles obtained in H_3PO_3-assisted reactions of indoles with nitrostyrenes.

Table 1 Optimization of spiro-cyclization towards **2aa**

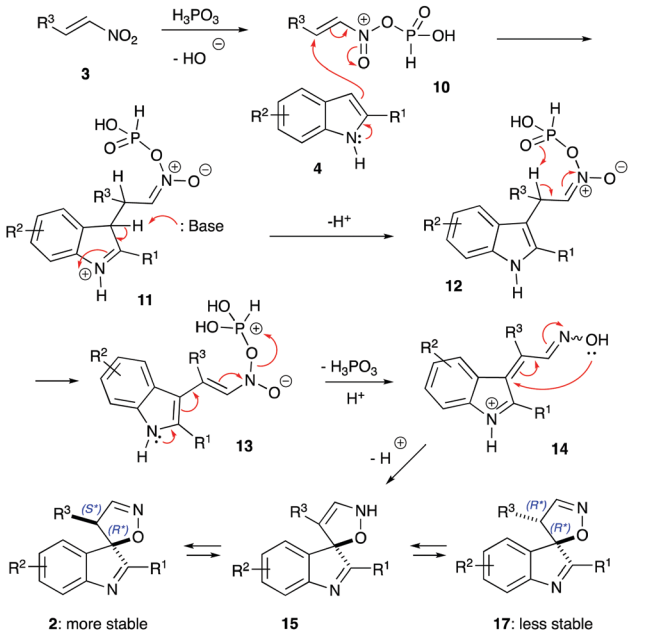


	Acid[a] (time, h)	**5aa**[c] (yield, %)	**2aa**[c] (yield, %)
1	CF_3COOH (1.5)	82	10
2	H_3PO_4 (1.5)	13	76
3	CH_3SO_3H (1.5)	60	8
4	H_2SO_4 (1.5)[b]	0	33
5	HCOOH (15)	83	8
6	H_3PO_3 (0.75)	0	98

[a] All acids were used as 1 : 1 mixture with 85% formic acid, unless specified otherwise. [b] A mixture of 150 mg of 98% sulfuric acid and 500 mg of 85% formic acid. [c] Yields were determined by ^{1}H NMR analysis of crude reaction mixtures.

the reaction is carried out for 45 min in H_3PO_3/HCOOH at room temperature (Scheme 3). It should be pointed out, that formation of **2aa** along with nitroalkane **5aa** (R = Ar = Ph) was observed in reaction between **3a** and **4a** in the presence of other strong Brønsted acids as well (Table 1). Weaker acids (such as acetic or benzoic) mediated Michael addition, affording **5aa** as sole product. At the same time, we also found that hydroxamic acid **6aa** (R = Ar = Ph) could not be converted into **2aa** under the same conditions, which proves that it does not serve as an intermediate in the featured transformation. Reaction in the presence of phosphorous acid (4 equiv.) provided nearly quantitative yield of **2aa** (Table 1, entry 6). It was also shown, that this cyclization can proceed in the presence of catalytic amounts of H_3PO_3 (10 mol%), but very slowly, requiring more than a weak to reach *ca.* 60% conversion. Provided relatively low cost of this catalyst, we decided to use it in excess.

With optimized conditions in hand, we moved on to explore the scope and limitations of this transformation. We first tested the reactivity of indole **4a** against nitrostyrenes bearing different substituents at C-4 (**3a–d**). All these reactions afforded the corresponding spiranes **2aa–2ad** in excellent yields (Scheme 3). Reactions of **4a** with nitro-olefins bearing primary (**3e**) or secondary (**3f**) alkyl substituents proved to be somewhat less efficient and sluggish, requiring 2 h for complete conversion, but the yields of the corresponding products **2ae** and **2af** were still reasonably high (Scheme 3). Reaction of **4a** with (*E*)-2-(2-nitrovinyl)furan (**3g**) allowed the preparation of 4′-(furan-2-yl)-substituted analog **2ag**, thus showing the possibility of introducing even acid-sensitive heteroaryl groups to the featured scaffold (Scheme 3). The reaction proved to be compatible with various aryl substituents at C-2 of the indole unit. Substrates bearing electron rich phenyl substituents (**4b**, **4d**) reacted smoothly affording the corresponding spiro-heterocycles **2ab–2ad** in excellent yields. Indoles bearing moderately electron poor aryl **4c** or 2-naphthyl (**4e**) substituents at C-2 reacted more sluggishly requiring extended reaction time (2 h), but still affording the corresponding products **2ca** and **2ea** quite efficiently. The introduction of heteroaryl substituents was also tolerated as demonstrated by the preparation of the thienyl



Scheme 4 Mechanistic rationale of the featured transformation.

substituted derivative **2fa** (Scheme 3). Replacing the phenyl group at C-2 with a methyl group resulted in very complex reaction mixtures and total decomposition of the initially formed spirocyclic product **2ga**. Lowering the temperature to 10 °C allowed for isolation of **2ga**, albeit in a marginal yield (Scheme 3). Also, it should be pointed out that 2-(trifluoromethyl)- (**4k**) and 2-(methoxycarbonyl)- (**4l**) 1*H*-indoles did not provide any spirocyclic products at all, even at 50 °C. Starting materials were recovered unchanged in both cases. Finally, we tested the possibility of introducing substituents in the aryl ring of the indole. 5-Isopropyl-2-phenyl-1*H*-indole (**4h**) reacted smoothly under standard reaction conditions with both nitrostyrenes **3a** and **3d** affording the corresponding products **2ha** and **2hd** in high yields. Likewise, reactions of 5-methoxy- (**4i**) and 7-chloro- (**4j**) substituted substrates allowed for the facile preparation of spirocyclic scaffolds **2ia** and **2ja**, respectively (Scheme 3).

Analysis of the obtained experimental data has led us to propose the following mechanistic rationale (Scheme 4). Exposure of nitrostyrene **3** to phosphorous acid makes it susceptible to Michael addition of indole **4**. The reduced nucleophilicity of indoles with electron-deficient substituents at C-2 at this stage explains unsuccessful reactions of substrates **4k** and **4l** (*vide supra*). Subsequent deprotonation at C3 of the indole in **11**, followed by intramolecular abstraction of a proton from the benzylic position by the phosphite ester of aci-nitro moiety in **12**, gives rise to *N*-phosphoryloxyenamine oxide species **13**. The latter, upon re-protonation, tautomerizes into hydroxylamine **14**. Next, acid-promoted 5-*endo-trig* cyclization of **14** takes place to give spiro-2,5-dihydroisoxazole species **15**,[13] which under the reaction conditions may tautomerize into either (3*R**,4′*S**)- (**2**) or (3*R**,4′*R**)-4,5-dihydroisoxazole **17**. Our DFT-modelling[14] suggests that the former one is thermodynamically favored by *ca.* 4.1 kcal mol^{-1}, which explains high diastereoselectivity of the featured transformation.[15] It should be stressed, that

proper acid–base balance is highly important for the successful spiro-cyclization. The acid should be sufficiently strong for initial activation of nitro-group in **3**, but at the same time it should be weak enough so it's conjugate base would be able to deprotonate species **12**.

In conclusion, nitroalkenes were successfully employed as synthetic equivalents of 1,4-dipoles of *CCNO*-type in a highly diastereoselective formal (4+1)-cycloaddition reaction of indoles in phosphorous acid to afford 4′*H*-spiro[indole-3,5′-isoxazole] derivatives **2**. Work for biological evaluation of spiro-heterocyclic systems **2** and synthetic application of these novel scaffolds is currently underway in our laboratories.

Financial support from Russian Science Foundation (Grant #18-13-00238) is gratefully acknowledged.

Conflicts of interest

There are no conflicts to declare.

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