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Construction of indeno[1,2-*b*]pyrroles *via* chemoselective *N*-acylation/cyclization/Wittig reaction sequence†

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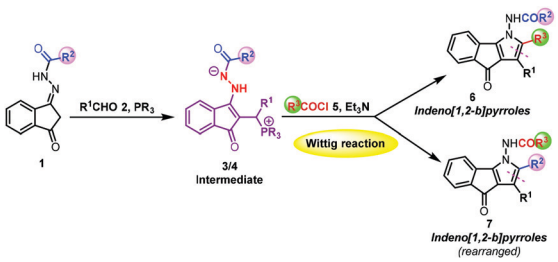
An efficient protocol for the chemoselective construction of the indeno[1,2-*b*]pyrroles and rearranged indeno[1,2-*b*]pyrrole derivatives is reported *via* an *N*-acylation/cyclization/Wittig reaction. Extensive mechanistic investigations revealed that the initially formed crucial spiro-indene-1,2′-[1,3,4]oxadiazol intermediate further reacts with phosphine to generate betaine, thus predominately resulting in the aforementioned heteroarenes proceeding by a Wittig reaction.

Phosphine-mediated transformations have enormous synthetic potential and are ubiquitous in organic synthesis due to the construction of a wide range of biologically active and medicinally important molecules.[1] Despite all of these transformations, the Wittig reaction has predominantly been explored to generate olefins in achieving a variety of high yielding and stereoselective reactions.[2] Consequently, it has witnessed its efficacy in multifaceted applications toward the preparation of vast libraries of heteroarenes and heterocyclic compounds with diverse skeletons.[3] Considering the prominence of this transformation, the development of various methods for providing multifarious privileged heterocyclic compounds is highly desirable.

On the other hand, indenopyrroles with a 6/5/5 framework containing a pyrrole core have shown remarkable biological activities,[4] and their derivatives have also been employed as antitumor activators, potent human protein kinase CK2 inhibitors, and breast cancer resistance protein ABCG2 inhibitors.[5] Methods for the synthesis of different types of indenopyrroles are well-explored,[6] but only a few synthetic methods regarding the preparation of indeno[1,2-*b*]pyrroles have been reported.[7] Owing to their significant pharmaceutical importance in the area of drug discovery, great efforts are being focused on the development of diverse methods for the efficient construction of indeno[1,2-*b*]pyrroles.

Earlier, the first method for direct β-acylation of 2-arylidene-1,3-indandiones with acyl chlorides catalyzed by organophosphanes has been reported from our laboratory.[8] The discovery of this reaction guided us to conduct several experiments and it was successfully extended to other cyclic and acyclic α,β-unsaturated carbonyl compounds to install the carbonyl functionality at the β-position.[9] In continuation of our pursuit of the exploration of organophosphane chemistry,[10] we were keen on the applications of indane-1,3-dione hydrazones toward the construction of multifarious heteroarenes. Herein, we wish to report an efficient synthesis of indeno[1,2-*b*]pyrroles and their rearranged adducts from the corresponding zwitterions with acyl chlorides and a base (Scheme 1). It is worth noting that the reaction of phosphorus zwitterions and acyl chlorides in the presence of a base exclusively resulted in the Wittig products instead of β-acylated adducts.

Initially, we started our investigation to prepare phosphorus zwitterions from the indane-1,3-dione hydrazones **1**, PBu_3, and various aldehydes **2** *via* a tandem three-component reaction.[10f] To our delight, the desired zwitterions **3a–3h** were obtained in high yields, irrespective of the nature and position of the



Scheme 1 Chemoselective Wittig approach towards the indeno[1,2-*b*]pyrroles **6/7**.

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† Electronic supplementary information (ESI) available: Synthetic procedures, characterisation data and copies of the spectra of all compounds. CCDC 2009731 (**3a**), 2016707 (**6aa**), 2009642 (**6ae**), 2009644 (**6ai**), 2009643 (**6aj**), 2009645 (**7ak**), 2009646 (**7ik**), 2009650 (**8aa**) and 2019535 (**8ak**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc08184a

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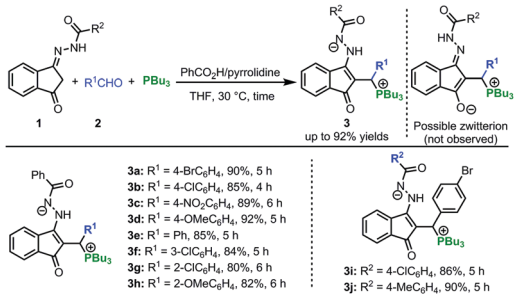
Table 1 Synthesis of functional zwitterions **3**[ab]

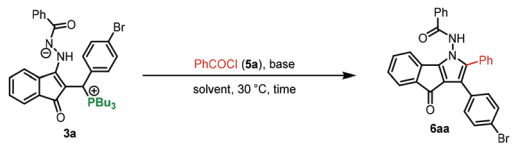


[a] The reactions were carried out with **1** (1.0 mmol), **2** (1.1 equiv.), $PhCO_2H$ (10 mol%), PBu_3 (1.2 equiv.), and pyrrolidine (10 mol%) in dry THF (10 mL) under argon at 30 °C. [b] Isolated yield.

substitution on the aryl ring (R^1) (Table 1). The substitution on different hydrazones **1** (R^2) also furnished the corresponding zwitterions **3i** and **3j** in good yields. The chemoselectivity of the reaction was realized with zwitterion **3** bearing a charge on the nitrogen atom rather than another possible zwitterion with charge on an oxygen atom. Further X-ray diffraction analysis unambiguously demonstrated the structure of the zwitterion **3a** with the charge on the nitrogen atom which is adjacent to the benzoyl group presumably; due to the electron-withdrawing capacity of the carbonyl group the charge will be delocalised over both the nitrogen and oxygen atoms of the amide like anion.[11a]

At first, we examined a reaction with phosphorus zwitterion **3a** and benzoyl chloride (**5a**) as model substrates in the presence of Et_3N in THF at 30 °C. Delightfully, the indeno[1,2-*b*]pyrrole derivative **6aa** was obtained in 85% yield in

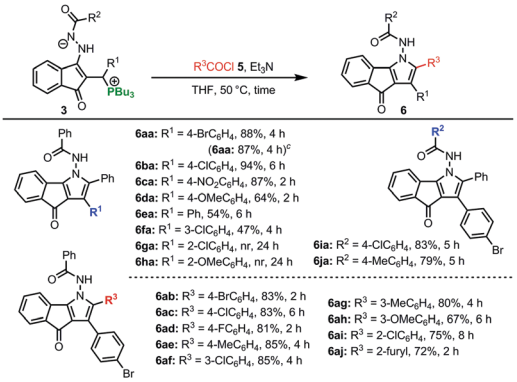
Table 2 Optimization of the reaction conditions[a]



Entry	Base	Solvent	t (h)	**6aa**[b]
1	Et_3N	THF	12	85
2	DIPEA	THF	18	60
3	DBU	THF	10	75
4	TMG	THF	10	51
5	TBD	THF	12	84
6	Et_3N	CH_2Cl_2	24	25
7	Et_3N	CH_3CN	24	50
8	Et_3N	Toluene	48	47
9	Et_3N	Et_2O	24	65
10[c]	Et_3N	THF	4	85
11[d]	Et_3N	THF	4	90
12[de]	Et_3N	THF	4	76

[a] The reactions were carried out with **3a** (0.1 mmol), **5a** (1.1 equiv.), and base (1.5 equiv.) in dry solvent (1 mL) under argon at 30 °C. [b] Yield of the product **6aa** was determined by NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] At 40 °C. [d] At 50 °C. [e] Addition sequence: **3a** (0.1 mmol), Et_3N (1.5 equiv.), and **5a** (1.1 equiv.).

Table 3 Substrate scope for the indeno[1,2-*b*]pyrroles **6**[ab]

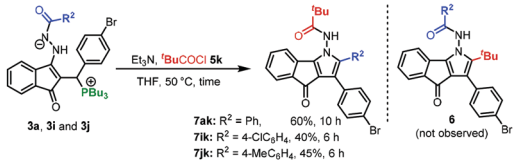


[a] The reactions were carried out with **3** (0.3 mmol), **5** (1.1 equiv.), and Et_3N (1.5 equiv.) in dry THF (3 mL) under argon at 50 °C. [b] Isolated yield. [c] Performed a gram-scale reaction (**3a**: 2 mmol, 1.267 g).

12 h (Table 2, entry 1). To find the optimal conditions, screening of different bases was carried out, and the product **6aa** was furnished in 51–84% yields in THF (entries 2–5). Next, various solvents were screened by using Et_3N as a base. The reaction in CH_2Cl_2 showed poor reactivity, providing the desired product **6aa** in only 25% yield even after 24 h (entry 6). Whereas other solvents like CH_3CN, toluene, and Et_2O afforded the product **6aa** in moderate yields, albeit requiring longer reaction times (entries 7–9). Interestingly, when the reactions were screened at 40 °C and 50 °C, the desired product **6aa** was obtained in 85% and 90% yields within 4 h, respectively (entries 10 and 11). Furthermore, a different addition sequence was also tested, but the results were not as efficient as previous conditions (entry 12). Finally, the optimal result was found by treating **3a** with **5a** in the presence of Et_3N in anhydrous THF at 50 °C as shown in entry 11.

Having found the optimal conditions, the substrate scope was further investigated (Table 3). First, the zwitterions bearing different R^1, and R^2 substitutions were subjected to PhCOCl (**5a**) under the standard conditions. Substrates with an electron-withdrawing group (R^1) at the *para*-position reacted with **5a** smoothly, furnishing the desired indeno[1,2-*b*]pyrroles **6aa–6ca** in up to 94% yields. It was found that the steric and electronic properties of the substituents have a significant effect on the reaction outcome. When the substrates **3d** (R^1 = 4-$OMeC_6H_4$) and **3e** (R^1 = Ph) participated in the reaction, the corresponding products **6da** and **6ea** were obtained in up to 64% yields. The substrate with Cl at the *meta*-position of R^1 (**3f**) was also tested to provide the desired product **6fa** in only moderate yield. The zwitterions bearing an *ortho*-substituted R^1, such as **3g** and **3h**, did not react with **5a** even when prolonging the reaction time up to 24 h, presumably due to the steric hindrance. Delightfully, zwitterions with different R^2 substitutions were well-tolerated, affording the corresponding products **6ia–6ja** in up to 83% yields.[11b]

Furthermore, various acyl chlorides **5** were tested in the reaction with zwitterion **3a**. Acyl chlorides bearing electron-withdrawing and electron-donating groups afforded the desired



Scheme 2 Synthesis of rearranged indeno[1,2-*b*]pyrroles **7**.

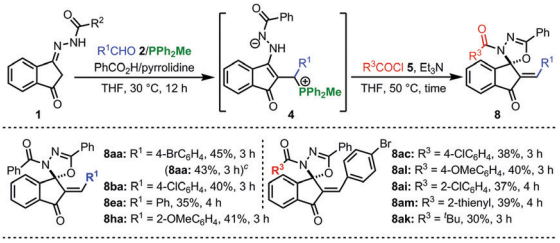
products **6ab–6ai** in up to 85% yields, irrespective of the nature and position of the substituents.[11b] Interestingly, the acyl chloride (**5j**) containing a heteroaryl group (2-furyl) was also well-tolerated, and the corresponding product **6aj** was obtained in 72% yield. In addition, to test the preparative utility of this chemoselective Wittig reaction, we performed a 2 mmol scale-up reaction using zwitterion **3a** and PhCOCl (**5a**). The desired indeno[1,2-*b*]pyrrole **6aa** was obtained in 87% yield with substantial quantity.

Accordingly, we also examined a reaction of aliphatic acyl chloride such as pivaloyl chloride (**5k**) with zwitterion **3a** under the optimal conditions. It was found that the rearranged indeno[1,2-*b*]pyrrole **7ak** was obtained in 60% yield instead of **6ak** (Scheme 2).[11a] Surprised by the results, the other zwitterions **3i** and **3j** were examined with **5k** under the same conditions. To our delight, zwitterions **3i** and **3j** also participated, albeit providing only moderate yields of the desired rearranged products **7ik** and **7jk**. Due to the low reactivity of pivaloyl chloride **5k**, the corresponding unreacted zwitterion **3** has also been recovered along with the rearranged indeno[1,2-*b*]pyrroles **7**. Notably, the acetyl chloride was also tested with **3a**, but the reaction did not furnish the desired products. It could be understood that when less reactive and hindered pivaloyl chloride **5k** was utilized as an acylating agent, rearranged products were realized *via* an intramolecular acyl group exchange/Wittig reaction sequence.[11b] This new approach of pivaloyl chloride utilized as an acyl group exchange precursor in the presence of a more reactive acyl group on hydrazones, can become a powerful tool to access diverse rearranged heteroarenes.

Next, we turned our attention to preparing the other phosphorus zwitterions **4** from the indane-1,3-dione hydrazones **1**, less nucleophilic PPh_2Me, and aldehydes **2** *via* a tandem three-component reaction.[10f] Unfortunately, we could not isolate the desired zwitterions **4** using column chromatography or even crystallization.[11c] To test the reactivity of zwitterions bearing PPh_2Me under our protocol, we have *in situ* generated the zwitterion **4a** and further reacted it with **5a** in the presence of Et_3N (Table 4). To our surprise, the spiro-indene-1,2′-[1,3,4]oxadiazol derivative **8aa** was obtained in 45% yield within 3 h, instead of indeno[1,2-*b*]pyrroles **6aa**/**7aa**. Furthermore, we have tested the different aldehydes **2** and acyl chlorides **5** with **1a** under the reaction conditions. All the tested substrates furnished the desired products in low to moderate yields in a one-pot manner. Probably, the instability of *in situ* generated zwitterion **4** could be the reason for the formation of the corresponding spiro products **8** in lower yields.

Two different types of products were found in our protocol by using the zwitterion bearing different phosphines. At an instance, we have assumed that the spiro-indene-1,2′-[1,3,4]oxadiazol

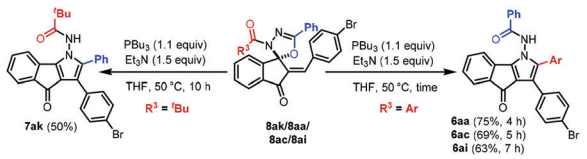
Table 4 Altering the reactivity of zwitterions by using PPh_2Me for the synthesis of **8**[ab]



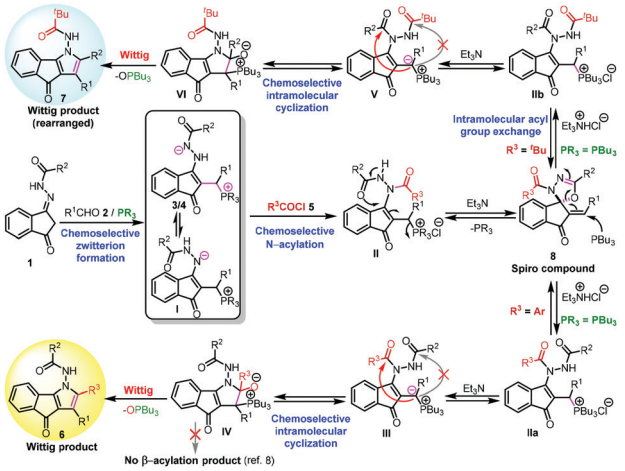
[a] The reactions were carried out with **1** (0.5 mmol), **2** (1.1 equiv.), $PhCO_2H$ (10 mol%), PPh_2Me (1.2 equiv.), and pyrrolidine (10 mol%) in dry THF (5 mL) under argon at 30 °C for 12 h. Afterwards, **5** (1.5 equiv.), and Et_3N (2.0 equiv.) were sequentially added, and the reaction was performed under argon at 50 °C. [b] Isolated yield. [c] Performed a gram-scale reaction (**1a**: 4 mmol, 1.057 g).

8 could be a possible intermediate for formation of the indeno[1,2-*b*]pyrrole. To test our hypothesis, we have examined the reactions of different spiro-indene-1,2′-[1,3,4]oxadiazols **8aa**, **8ac**, and **8ai** with PBu_3 in the presence of Et_3N. To our delight, the desired indeno[1,2-*b*]pyrroles **6aa**, **6ac**, and **6ai** were obtained in up to 75% yields within 4–7 h (Scheme 3).[11b] Furthermore, the acyl transfer reaction has been investigated in the case of spiro compound **8ak** with PBu_3. Remarkably, the rearranged indeno[1,2-*b*]pyrrole **7ak** was also found in the reaction with 50% yield.[11b] This clearly indicates that PBu_3 with higher nucleophilicity could further react with **8** to result in the indeno[1,2-*b*]pyrrole **6** or **7**, depending on the relative reactivities of acylating agents.

Based on the above results, a plausible mechanism is depicted in Scheme 4. Initially, a chemoselective tandem three-component reaction of indane-1,3-dione hydrazone **1**, aldehyde **2**, and phosphine furnished the phosphorus zwitterion **3**/**4** which could be interchangeable with another possible zwitterion **I**. The chemoselective *N*-acylation of the zwitterion **I** with acyl chloride **5** would generate phosphonium salt **II** that can easily cyclize to give the spiro compound **8** *via* allylic substitution with elimination of PR_3. When the eliminated PR_3 has less nucleophilic nature such as PPh_2Me, only the spiro compound **8** would be provided. Instead, a more nucleophilic PR_3, such as PBu_3, would further react with **8** to generate the phosphonium salt **IIa**. The deprotonation of **IIa** by Et_3N generates ylide **III**, and subsequent chemoselective intramolecular Wittig reaction upon **III** would lead to the indeno[1,2-*b*]pyrrole **6** *via* the formation of a crucial betaine **IV**. On the other hand, the less reactive and hindered pivaloyl group present on the spiro compound **8** would facilitate the intramolecular acyl group exchange to generate the



Scheme 3 Control experiments for the conversion of **8** to **6**/**7**.



Scheme 4 Plausible mechanism.

phosphonium salt **IIb**, and that would provide ylide **V** in the presence of Et_3N. Furthermore, a chemoselective intramolecular Wittig reaction upon ylide **V** would result in the rearranged indeno[1,2-*b*]pyrrole **7**. Although the exact factors leading to acyl group exchange are not clear, it was presumed on the basis of our results and control experiments (see Table 4, and Scheme 3).[11d] It is worth noting that the rearrangement reaction was not efficient to furnish the β-acylated products in both cases, which was probably due to the lower C–N than C–O bond lability of the corresponding betaines.

In summary, we have demonstrated a novel method for the synthesis of indeno[1,2-*b*]pyrroles *via* a chemoselective zwitterion formation/*N*-acylation/cyclization/Wittig reaction sequence. A series of phosphorus zwitterions were prepared and could be utilized for the synthesis of multifarious heteroarenes in moderate to high yields. Furthermore, an unprecedented intramolecular acyl group exchange/chemoselective Wittig reaction was realized for synthesis of the rearranged indeno[1,2-*b*]pyrroles. In addition, we have found a spiro-indene-1,2′-[1,3,4]oxadiazol as a crucial intermediate by choosing an appropriate zwitterion with PPh_2Me, and it could easily be transformed into indeno[1,2-*b*]pyrroles **6**/**7**.

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Conflicts of interest

There are no conflicts to declare.

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11 See the ESI† for(*a*) the detailed characterization of the products including X-ray diffraction analysis; (*b*) the compounds in Table 3 (**6ia**, **6ja**, and **6ab–6aj**), Scheme 2 (**7ik**, and **7jk**), and Scheme 3 (**6aa**, **6ac**, **6ai**, and **7ak**) further confirmed by the EIMS analysis; (*c*) the formation of zwitterion **4a** confirmed by ^{31}P NMR and HRMS analysis of the crude reaction mixture; (*d*) the detailed intramolecular acyl group exchange reaction mechanism.

