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Unprecedented Rearrangement of 2-(2-Aminoethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]indazole-2-ium 6-oxides to 2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazoles

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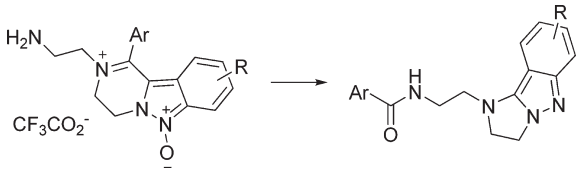
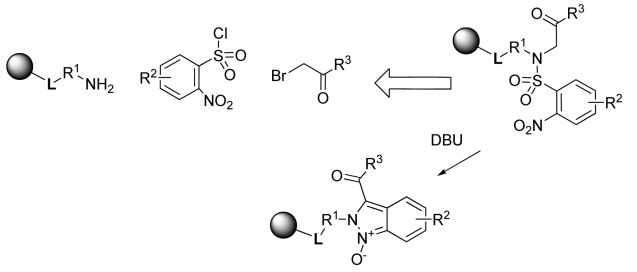


Easily accessible 2-(2-aminoethyl)-1-aryl-3,4-dihydropyrazino-[1,2-*b*]indazole-2-ium 6-oxides rearranged to 2,3-dihydro-1*H*-imidazo[1,2-*b*]indazoles under mild conditions. The rearrangement appeared to be general, tolerated a wide range of functional groups, and provided access to an as yet unexplored class of heterocycles. Herein we report the characterization of these heterocycles.

In continuation of our search for novel and efficient routes to pharmacologically relevant heterocyclic compounds we discovered a process for tandem carbon−carbon followed by nitrogen−nitrogen bond formation yielding indazole oxides (Scheme 1) of excellent purity.[1]

Synthetic compounds comprising the indazole core have recently become an increasingly frequent subject of biological studies. A review article by Cerecetto and colleagues[2] portrayed the diversity of biological activities exhibited by indazoles: recent advances in the chemistry of indazoles were reviewed by Schmidt and colleagues.[3] Since then, numerous new studies identified indazole-based compounds as potent

SCHEME 1. Synthesis of Indazole Oxides[1]



agents with anti-inflammatory, anticancer,[4−6] antimicrobial,[7,8] antifungal,[9,10] and cytotoxic[11] activities.

Indazoles were found to be potent inhibitors of nitric oxide synthetase,[12−14] factor Xa,[15] protein kinases,[16,17] tubulin,[18] reverse transcriptase,[19] vascular endothelial growth factor receptor,[20] and TRPV1.[21,22] Indazoles were active as male contraceptives[23,24] and 5-HT2C receptor agonists.[25]

A wide range of biological activities prompted us to extend our indazole chemistry for traceless solid-phase synthesis of pyrazino[1,2-*b*]indazoles[26] and 2-(2-aminoethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]indazole-2-ium 6-oxides.[27] Heterocycles were synthesized in a very efficient three-step

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procedure on solid phase under mild conditions with use of commercially available building blocks: amines, 2-nitrobenzenesulfonyl chlorides, and bromoketones.

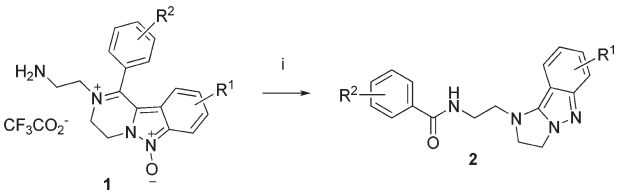
Here, we report an unprecedented rearrangement of 2-(2-aminoethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]indazole-2-ium 6-oxides to 2,3-dihydro-1*H*-imidazo[1,2-*b*]indazoles, formally involving concomitant 5-membered ring-opening, 6- to 5-membered ring contraction, amide formation, and deoxygenation. The rearrangement proceeded quantitatively under mild conditions and provided a route to a very efficient synthesis of this class of thus far unexplored heterocycles. 2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazoles have not been reported in the literature and we found only one report related to our fused heterocycles that described the synthesis of benzimidazoindazoles[28] and oxazolo[3,2-*b*]indazoles.[29]

During the isolation of 2-(2-aminoethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]indazole-2-ium 6-oxides, prepared following our recently published procedure,[27] we observed a quantitative rearrangement of the targeted compounds. Indazole oxide derivative **1(1,1)** (R^1 = H, and R^2 = Me, refer to Table 2 for notation), prepared with 2-nitrobenzenesulfonyl chloride and 2-bromo-1-*p*-tolylethanone, was purified on semipreparative HPLC, using aqueous ammonium acetate buffer and acetonitrile. The purified compound was isolated after solvent evaporation at elevated temperature (50 °C) and freeze-drying. The LCMS analysis of supposedly purified compound revealed that the target compound had transformed to a new product that exhibited an identical mass spectrum. However, the retention time had changed; the new compound was more hydrophobic. Its UV spectrum was nearly identical with that of compound **1(1,1)**. We isolated and fully characterized the unexpected product by 1D and 2D NMR spectroscopy and high-resolution MS. In addition, we were able to crystallize the product from acetonitrile solution and its structure was determined by a single-crystal X-ray diffraction study (figure in the Supporting Information). The structure of the rearranged product was 2,3-dihydro-1*H*-imidazo[1,2-*b*]indazole derivative **2(1,1)** (Scheme 2).

This unexpected and very clean (and thus potentially very useful from the preparative point of view) rearrangement prompted a focused study of this transformation reaction. The model experiments were carried out with indazole oxide derivative **1(1,1)**.

Solutions of **1(1,1)** in 50% aqueous acetonitrile were subjected to seven reaction conditions and the conversion of **1(1,1)** to **2(1,1)** was monitored by LCMS analysis. A solution containing 10 mM ammonium acetate was heated to 50 °C for 16 h and a quantitative conversion to **2(1,1)** was observed (Table 1). A solution containing 0.1% TFA, typically used for HPLC purification, was completely stable under identical conditions. The data indicated that solutions at pH above 7 caused a quantitative conversion to **2(1,1)**. Crude preparations of **1**, obtained after TFA/DCM cleavage from resin and evaporation of TFA and DCM, still contained residual TFA. Therefore, for practical syntheses of **2**, pH of the solution was adjusted with a saturated solution of sodium carbonate and exposed to elevated temperature.

SCHEME 2. Rearrangement of Indazoles 1[a]



[a]Reagents and conditions: (i) 50% acetonitrile in 10 mM aqueous ammonium acetate, 16 h, for temperature, cf, Table 2.

TABLE 1. The Effect of a Base on Conversion to the Rearranged Product 2[a]

		conversion (%)	
entry	aq solution	21 °C, 15 min	50 °C, 16 h
1	10 mM NH_4OAc	NT	100
2	0.1% TFA	NT	0
3	10 mM TFA, 10 mM NH_4OAc	1	5
4	10 mM TEA, 10 mM HOAc	50	100
5	10 mM NaOAc	10	100
6	10 mM $NH_2OH \cdot HCl$	1	5
7	entry 3 plus satd soln Na_2CO_3	1	100

[a]Note: The compound **1(1,1)**, ~0.6 mg, was dissolved in 200 μL of acetonitrile and 200 μL of aqueous solution was added.

To assess the scope and limitation of the rearrangement, we prepared a set of compounds with building blocks containing both electron-donating and electron-withdrawing groups. The reaction conditions, temperature and time, for individual compounds are listed in Table 2. The course of the reaction and formation of the rearranged product was monitored by both LC and ^{1}H NMR. A few of the products, **2(2,3)**, **2(3,3)**, **2(2,5)**, and **2(3,5)**, eluted very close to their corresponding precursors (Table 2) and monitoring of completion of the rearrangement by LC was problematic. ^{1}H NMR spectra were collected to reliably determine completion of the reaction. ^{1}H NMR spectra exhibited typical signals for two methylene groups of the constituent aliphatic chain (two triplets in the area 4.5−4.0 ppm) and a triplet at 8.5 assigned to the NH proton. The ^{13}C NMR spectrum revealed the typical C=O resonance at δ 164−166 ppm and it was used as the indicator for the formation of the products.

All combinations of building blocks afforded the corresponding rearranged products. The analytical data indicated that the rates of the conversions were not significantly influenced by the R^1 substituent. The effect of the R^2 substituent was more pronounced. The rearrangement was complete to give compounds **2** with electron-donating groups (R^2 = 4-Me, 4-OMe) and 4-Cl (R^1 = CF_3, NO_2) at 50 °C. To observe complete transformation of derivatives **2** with R^2 = 4-Cl (R^1 = H), 4-CN, the temperature was

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TABLE 2. The Effect of R^1 and R^2 on Formation of 2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazoles 2[a]

entry	R^1	R^2	*T* (°C)	Rt of **1**[a]	Rt of **2**[a]	purity[b] (%)	yield (%)
2(1,1)	H	4-Me	50	5.13	5.70	86	53
2(1,2)	H	4-OMe	50	4.52	5.25	97	65
2(1,4)	H	4-CN	80	4.58	5.13	58	26
2(1,5)	H	−[c]	80	5.23	5.75	83	50
2(2,2)	4-CF_3	4-OMe	50	6.23	6.58	94	71
2(2,3)	4-CF_3	4-Cl	50	7.30	7.52	76	37
2(2,4)	4-CF_3	4-CN	80	6.15	6.47	79	23
2(2,5)	4-CF_3	−[c]	80	6.87	6.97	85	67
2(3,2)	4-NO_2	4-OMe	50	5.47	5.80	94	53
2(3,3)	4-NO_2	4-Cl	50	6.57	6.77	87	41
2(3,4)	4-NO_2	4-CN	80	5.37	5.75	72	41
2(3,5)	4-NO_2	−[c]	80	6.15	6.18	89	52

[a]Retention time (min) on analytical C18 column (for conditions, cf. the Supporting Information). [b]Calculated from UV response on LC traces at 200−400 nm. [c]R^2 = 3,5-diCl-4-NH_2.

elevated to 80 °C. The LC results showed that, although the products **2(1,1)** and **2(1,5)** were complete after 3.5 and 2 h, respectively, the conversion of compounds **1(R[1],3)** was only 40% to 70% after 3 h, hence they were allowed to react overnight.

Starting materials and products of compounds **2(2,5)** and **2(3,5)** eluted close to each other and ^{1}H NMR spectra, recorded after overnight reaction, confirmed quantitative rearrangement. Analyses of LC traces and ^{1}H NMR spectra confirmed that the rearrangements were very clean. The only minor impurities we detected were present in 1−7% with respect to the products and gave MS spectra with ions of *m*/*z* −15, which may supposedly belong to deoxygenated products formed during indazole cyclizations and subsequent rearrangements.

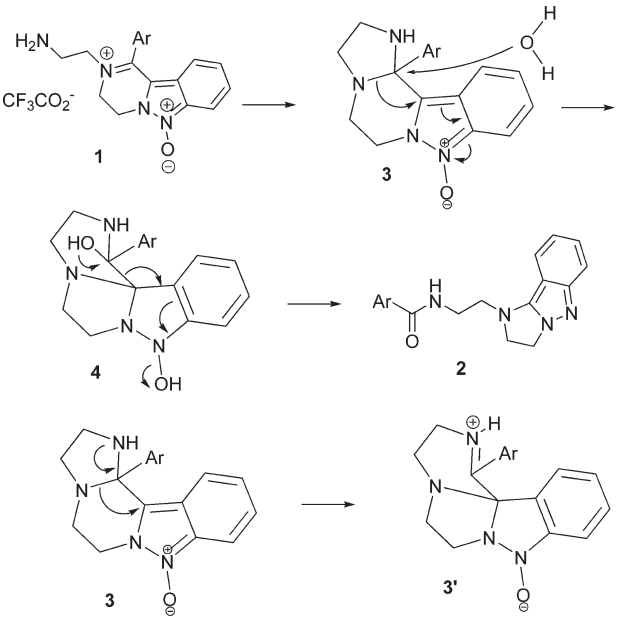
We propose the following mechanistic explanation of the rearrangement (Scheme 3). In neutral pH, the iminium **1** closed a five-membered ring and formed the imidazolidine derivative **3**.[27] This rearrangement was triggered by an initial formation of a carbon−oxygen bond by nucleophilic attack at the quaternary carbon by water with concurrent ring contraction and formation of imidazolidine **4**. The formation of this new carbon−nitrogen bond was facilitated by the presence of the *N*-oxide, responsible for electronic activation of the electron-deficient nitrogen. Formation of *N*-hydroxy derivative **4** was the critical step toward water elimination that stabilized the intermediate structure by rearomatization of the indazole core and formation of carboxamide **2**.

An alternative reaction mechanism, suggested by one of the reviewers, included formation of an intermediate **3′**, followed by the water attack.

To confirm the essential role of the *N*-oxide, we prepared the deoxygenated analogue of **1** using methanesulfonyl chloride and triethylamine.[30] After two days of heating in ammonium acetate solution at 50 °C no change of the deoxygenated material was observed.

To conclude, we report an unprecedented formation of 2,3-dihydro-1*H*-imidazo[1,2-*b*]indazoles by rearrangement formally involving 5-membered ring-opening, 6- to 5-membered ring contraction, amide formation, and deoxygenation. In several examples, the rearrangements proceeded

SCHEME 3. Proposed Mechanism of 2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazoles Formation



cleanly under mild conditions and tolerated a wide range of substitution pattern on both aromatic rings. 2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazoles can be regarded as 2,3-substituted-2*H*-indazoles with an additional ring closed between substituents at positions 2 and 3. Synthetic compounds comprising indazole core have recently become an increasingly frequent subject of biological studies: indazole derivatives possessed significant potency in a wide range of diverse biological targets.[2]

Experimental Section

2-(2-Aminoethyl)-1-aryl-3,4-dihydropyrazino[1,2-*b*]indazole-2-ium 6-Oxides 1. Synthesis of **1** was carried out on solid phase as described previously.[27] After finishing the solid-phase synthesis, products were cleaved from the resin with 50% TFA/DCM for 1 h. The TFA solution was collected. The resin was washed with 50% TFA/DCM (3×) and combined extracts were evaporated by a stream of nitrogen.

2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazoles 2. After cleavage from the resin, the crude oily residue, typically ∼100 mg, was dissolved in 3 mL of acetonitrile then diluted with 3 mL of 10 mM aqueous ammonium acetate and the pH was adjusted to 8 by addition of a saturated solution of Na_2CO_3. The resulting solution was heated to 50−80 °C for 16 h. Solvents were evaporated under reduced pressure. The oily residue was dissolved in a minimum volume of acetonitrile and purified by semipreparative reversed phase HPLC in a gradient formed from acetonitrile and 10 mM aqueous ammonium acetate. Products were collected after freeze-drying.

***N*-(2-(2,3-Dihydro-1*H*-imidazo[1,2-*b*]indazol-1-yl)ethyl)-4-methoxybenzamide 2(1,2).** Yield (HPLC purified) 27.3 mg (65%). ESI-MS *m*/*z* 337 $[M + H]^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (t, J = 5.6 Hz, 1 H), 7.75−7.81 (m, 2 H), 7.61 (d, J = 8.4 Hz, 1 H), 7.27 (d, J = 8.8 Hz, 1 H), 7.06 (ddd, J = 1.1, 6.6, 8.9 Hz, 1 H), 6.94−6.99 (m, 2 H), 6.72 (ddd, J = 0.9, 6.6, 8.5 Hz, 1 H), 4.38 (t, J = 8.4 Hz, 2 H), 4.00 (t, J = 8.4 Hz, 2 H), 3.79 (s, 3 H), 3.52−3.59 (m, 4 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.0, 161.5, 152.5, 147.4, 128.9, 126.6, 125.6, 119.6, 117.1, 116.7, 113.4, 103.8, 55.3,

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54.5, 49.4, 46.5, 37.7 HRMS (FAB) *m*/*z* calcd for $C_{19}H_{21}N_4O_2$ $[M + H]^+$ 337.1665, found 337.1666.

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Supporting Information Available: Spectroscopic and crystallographic data and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.