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A Novel Approach to 1*H*-Indazoles *via* Arylazosulfides

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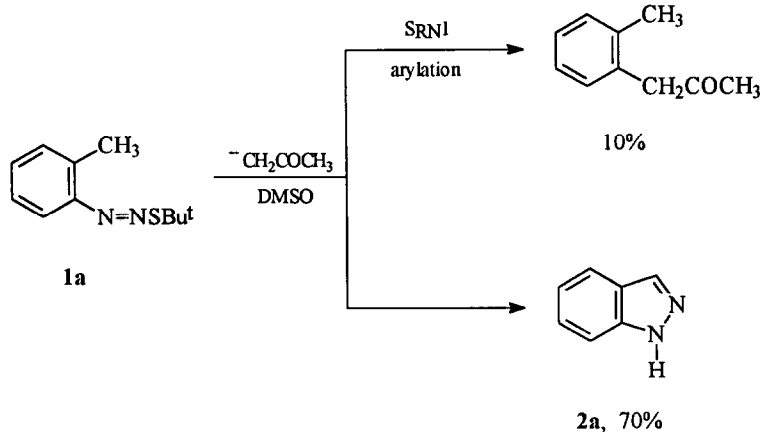
Abstract: Treatment of variously substituted (*o*-alkylaryl)azosulfides **1a-n** with potassium *tert*-butoxide in DMSO at room temperature smoothly furnishes 1*H*-indazoles **2a-n**.

In the context of a long-standing exploitation of azosulfides as efficient arylating agents towards carbon nucleophiles[1] we have recently reported that a methyl group *ortho* to the azothio function, as in **1a**, makes the formation of 1*H*-indazole (**2a**) a powerful competitor of the expected $S_{RN}1$ arylation of acetone enolate in DMSO (Scheme 1).[1f]

Scheme 1



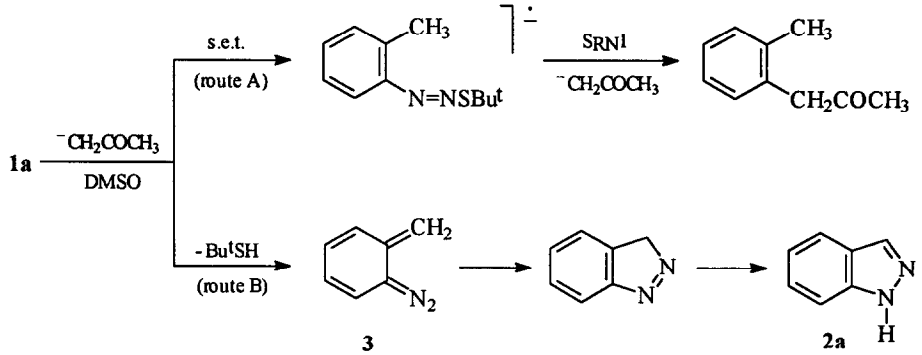
Preliminary experiments[2] have proved very encouraging as to the versatility of *o*-alkylsubstituted arylazosulfides as precursors of indazoles which represent a class of compounds of broad interest particularly in the biological and pharmacological fields,[3,4] due to their incorporating a pyrazole nucleus or, more specifically,

as indole bioisosteres.[4] The work herein was accordingly intended to better define the scope and limitations of such an appealing heterocyclization approach: it seems worthwhile recalling that, against a background of methods essentially plagued with the lack of generality,[5-9] the overall most convenient route to 1*H*-indazoles is so far provided by a crown-ether-catalyzed basic cyclization of *ortho*-alkylbenzenediazonium tetrafluoroborates.[10,11]

RESULTS AND DISCUSSION

A rationalization of the results of Scheme 1 has been offered,[1f] based (Scheme 2) on the dual behavior of acetone enolate as a one-electron reductant towards **1a** or as an effective base towards benzylic hydrogens whose intrinsic acidity is enhanced by the *ortho* electron-accepting azothio group. The former behavior would trigger the $S_{RN}1$ propagation cycle to the arylation product [route A]; the latter would lead instead, *via tert*-butanethiol elimination, to the methylidenediazocyclohexadiene intermediate **3** [route B], the following

Scheme 2

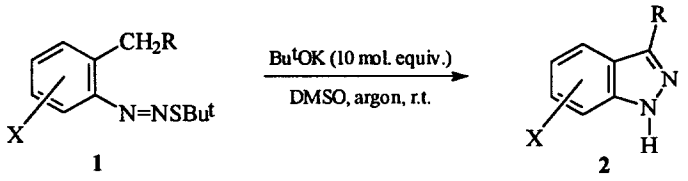


intramolecular cyclization straightforwardly accounting for the final 1*H*-indazole.

Scheme 2 implies that any reducing species would have a detrimental effect on the indazole yield and optimization of the yield of **2a** (84%) has been herein accordingly achieved by reacting **1a** with excess Bu^{t}OK in DMSO (Table 1, entry 1). In the absence of strong electron-withdrawing groups on the aryl moiety of the substrate, the same system has proved to be well suited for a whole series of (*ortho*-alkylaryl)azosulfides and the results in Table 1 clearly show that the simplicity of the method effectively couples with yields which are generally more than satisfactory and always higher or at least comparable with those from the cited PTC procedure.[10a]

Special interest lies in the results of experiments 12-14 of Table 1, where 3-substituted indazoles are obtained from azosulfides **1l-n**. The reaction on the *ortho*-allyl derivative **1n** (entry 14) deserves, in particular, a closer attention: it actually affords almost quantitatively 3-vinylindazole (**2n**), whose exocyclic double bond makes it an intermediate for the synthesis of variously 3-functionalized indazoles. On these grounds, the possibility, by us successfully verified, to scale-up the synthesis of **2n** without major complications and/or any

Table 1. Results for the reaction:



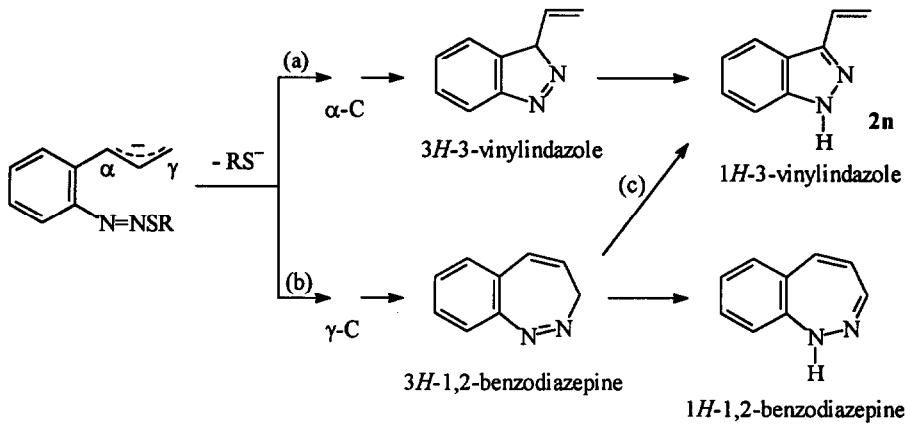
Entry	Azosulfide, X	R	Time (h)	Yield (%)[a]	Indazole, X
1	**1a**, H	H	1	84	**2a**, H
2	**1b**, 3-Me	H	1.5	94	**2b**, 4-Me
3	**1c**, 4-Me	H	1.5	46	**2c**, 5-Me
4	**1d**, 5-Me	H	1.5	86	**2d**, 6-Me
5	**1e**, 4,6-Me_2	H	1.5	58	**2e**, 5,7-Me_2
6	**1f**, 4-OMe	H	6	73	**2f**, 5-OMe
7	**1g**, 4-Cl	H	2	> 98	**2g**, 5-Cl
8	**1h**, 5-Cl	H	24	95	**2h**, 6-Cl
9	**1i**, 6-Cl	H	1.5	> 98	**2i**, 7-Cl
10	**1j**, 4-Br	H	1.5	98	**2j**, 5-Br
11	**1k**, 4-Br-6-Me	H	1.5	76	**2k**, 5-Br-7-Me
12	**1l**, H	Me	1	74	**2l**, H
13	**1m**, H	Et	1.5	79	**2m**, H
14	**1n**, H	$CH=CH_2$	1.5	93	**2n**, H

[a]Yields refer to isolated, chromatographically pure products.

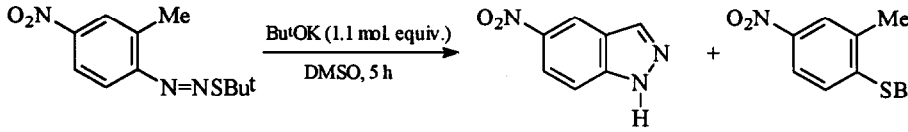
sizeable yield decrease seems by no means trivial. Mechanistically, the exclusive formation of 3-vinylindazole reveals, furthermore, a marked selectivity of a process which could in principle competitively lead to a 7-membered diazepine ring through the involvement of the γ-carbon in the intramolecular cyclization step [Scheme 3, path (b)]. A rationale for this outcome is possibly represented by the higher stability of the fully aromatic indazole system; it is worth recalling, at this regard, that 3*H*-1,2-benzodiazepines have been shown to promptly undergo a rearrangement to 3-vinylindazoles by heat- or light-stimulation:[12] although the experimental conditions herein do not meet such requirements, the participation of pathway (b) + (c) of Scheme 3 cannot be completely excluded.

As to the applicability field of the heterocyclization herein, the presence of nitro groups on the aryl moiety of the azosulfide enforces a more careful tuning of experimental conditions such as the strength and/or

Scheme 3

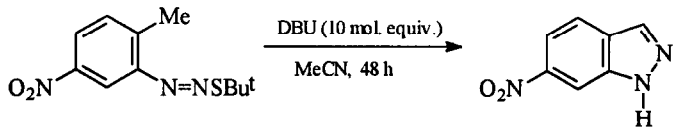


the reducing power of the base. As a matter of fact, with both the 4-nitro- (**1o**) and the 5-nitro-2-methylphenylazo (**1p**) sulfides no indazole could be obtained in the usual conditions, as a result of a fast formation of tars, possibly due to reductive processes brought about by Bu^{t}OK itself. In the case of **1o** the yield of the relevant 5-nitroindazole (**2o**) sizeably increases when lowering the base to substrate ratio (eq. 1), although the formation of *tert*-butyl 2-methyl-4-nitrophenyl sulfide (**4**), most likely *via* the $S_{RN}1$ mechanism,[1a,e] still proves to be highly competitive.



1o **2o**, 38% **4**, 41% (1)

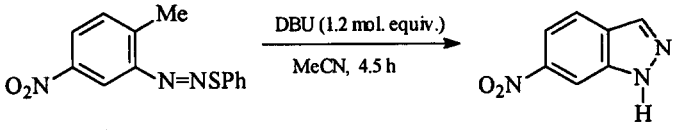
On the other hand, the weaker base DBU effectively accomplishes deprotonation of the more acidic benzylic hydrogens of **1p**, apparently avoiding major complications deriving from electron-transfer processes (eq. 2), and the yield of 6-nitroindazole (**2p**) becomes practically quantitative when the S-*tert*-butyl azosulfide is replaced with the S-phenyl analogue (**5**) (eq. 3).[13]



1p **2p**, 54%(*) (2)

(*)Unreacted substrate (16%) also recovered.

However, the use of DBU on either (2-methyl-4-nitrophenyl)azo phenyl or *tert*-butyl sulfide is uneffective as to the formation of **2o**, indicating lack of generality of the method herein when applied to nitrosubstituted arylazosulfides.



5 **2p**, > 98% (3)

CONCLUSIONS

The results in Table 1 demonstrate the significance of the present indazole synthesis from arylazosulfides **1** insofar as, using very simple experimental conditions, good yields can be achieved for a wide range of differently substituted substrates. On the other hand, nitroderivatives undoubtedly set a limit to the applicability of the process and, notwithstanding the result of eq. 3, the most convenient access to nitroindazoles is still represented by the long-known cyclization in acidic conditions of the diazonium salts arising from nitrosubstituted *o*-toluidines.[5a,b,14]

EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus and are uncorrected. ^{1}H nmr spectra were taken in $CDCl_3$ (if not otherwise stated) on a Varian Gemini 200 spectrometer; TMS was used as internal standard and chemical shifts are reported as δ values (ppm).

Materials

Petroleum ether and light petroleum refer to the fractions with bp 40-60 °C and 80-100 °C, respectively. Dimethylsulfoxide (Fluka) and acetonitrile (BDH) were used as received after storage over molecular sieves (4 Å). Potassium *tert*-butoxide (Aldrich, 97%) and DBU (Fluka) were employed without further purification. Arylamines, used for the synthesis of azosulfides, were all commercially available (used as received) but for 2-allylaniline, which was synthesized through a reported procedure[15] from commercial *N*-allylaniline.

Arylazosulfides

(*Z*)-Arylazo *tert*-butyl sulfides and (*E*)-arylazo phenyl sulfides were synthesized according to a reported procedure.[16] Crude products were obtained either by filtration and careful washing with cold MeOH or by extraction into Et_2O and were purified by flash-chromatography (silica gel; petroleum ether and gradients with CH_2Cl_2 as eluants) and/or crystallization in the cold; such samples were used throughout for the experiments

herein, due to their satisfactory degree of purity (tlc, ^{1}H nmr). No attempts have been made to attain analytically pure samples. Physical and/or spectroscopic data relevant to *tert*-butyl (2-methylphenyl)azo sulfide (**1a**) and to *tert*-butyl (2,4,6-trimethylphenyl)azo sulfide (**1e**) and have been previously reported.[1f]

tert-Butyl (2,3-dimethylphenyl)azo sulfide (**1b**): orange oil; ^{1}H nmr: δ 1.59 (9H, s), 2.01 (3H, s), 2.32 (3H, s), 6.64 (1H, m) and 7.15 (2H, m).

tert-Butyl (2,4-dimethylphenyl)azo sulfide (**1c**): orange oil; ^{1}H nmr: δ 1.59 (9H, s), 2.11 (3H, s), 2.34 (3H, s), 6.71 (1H, d, *J* 8.6 Hz) and 7.06 (2H, m).

tert-Butyl (2,5-dimethylphenyl)azo sulfide (**1d**): orange oil; ^{1}H nmr: δ 1.59 (9H, s), 2.07 (3H, s), 2.34 (3H, s), 6.58 (1H, br s), 7.03 (1H, dd, *J* 1.3 and 7.9 Hz) and 7.14 (1H, d, *J* 7.9 Hz)

tert-Butyl (4-methoxy-2-methylphenyl)azo sulfide (**1f**): orange oil; ^{1}H nmr: δ 1.60 (9H, s), 2.17 (3H, s), 3.81 (3H, s) and 6.80 (3H, m).

tert-Butyl (4-chloro-2-methylphenyl)azo sulfide (**1g**): orange oil;[17] ^{1}H nmr: δ 1.60 (9H, s), 2.11 (3H, s), 6.74 (1H, d, *J* 8.1 Hz) and 7.23 (2H, m).

tert-Butyl (5-chloro-2-methylphenyl)azo sulfide (**1h**): orange oil; ^{1}H nmr: δ 1.60 (9H, s), 2.08 (3H, s), 6.78 (1H, br s) and 7.19 (2H, app d).

tert-Butyl (6-chloro-2-methylphenyl)azo sulfide (**1i**): orange oil; ^{1}H nmr: δ 1.61 (9H, s), 2.07 (3H, s), 7.14 (2H, m) and 7.28 (1H, m).

(4-Bromo-2-methylphenyl)azo *tert*-butyl sulfide (**1j**): orange oil; ^{1}H nmr: δ 1.60 (9H, s), 2.10 (3H, s), 6.68 (1H, d, *J* 8.2 Hz) and 7.38 (2H, m).

(4-Bromo-2,6-dimethylphenyl)azo *tert*-butyl sulfide (**1k**): mp 94.1–95.3 °C; ^{1}H nmr: δ 1.60 (9H, s), 2.00 (6H, s) and 7.22 (2H, br s).

tert-Butyl (2-ethylphenyl)azo sulfide (**1l**): orange oil; ^{1}H nmr: δ 1.16 (3H, t, *J* 7.6 Hz), 1.60 (9H, s), 2.49 (2H, q, *J* 7.6 Hz), 6.80 (1H, m) and 7.27 (3H, m).

tert-Butyl (2-propylphenyl)azo sulfide (**1m**): orange oil; ^{1}H nmr: δ 0.91 (3H, t, *J* 7.3 Hz), 1.56 and 1.59 (11H in all, s and m overlapped), 2.45 (2H, t, *J* 7.7 Hz), 6.83 (1H, m) and 7.25 (3H, m).

(2-Allylphenyl)azo *tert*-butyl sulfide (**1n**): orange oil; ^{1}H nmr: δ 1.59 (9H, s), 3.24 (2H, m), 5.05 (2H, m), 5.88 (1H, m), 6.84 (1H, m) and 7.27 (3H, m).

tert-Butyl (2-methyl-4-nitrophenyl)azo sulfide (**1o**): mp 59.1–60.2 °C; ^{1}H nmr: δ 1.62 (9H, s), 2.21 (3H, s), 6.91 (1H, d, *J* 8.6 Hz) and 8.15 (2H, m).

tert-Butyl (2-methyl-5-nitrophenyl)azo sulfide (**1p**): mp 60.5-62.5 °C; ^{1}H nmr: δ 1.62 (9H, s), 2.23 (3H, s), 7.44 (1H, d, *J* 8.4 Hz), 7.68 (1H, d, *J* 2.3 Hz) and 8.09 (1H, dd, *J* 2.3 and 8.4 Hz).

(2-Methyl-4-nitrophenyl)azo phenyl sulfide: mp 95.9-97.1 °C; ^{1}H nmr: δ 2.56 (3H, s), 7.32 (1H, d *J* 8.8 Hz), 7.53 (3H, m), 7.67 (2H, m), 8.03 (1H, dd, *J* 2.5 and 8.8 Hz) and 8.15 (1H, d, *J* 2.5 Hz).

(2-Methyl-5-nitrophenyl)azo phenyl sulfide (**5**): mp 70.1-71.0 °C (dec.) (toluene/petroleum ether); ^{1}H nmr: δ 2.58 (3H, s), 7.42 (1H, d, *J* 8.8 Hz), 7.53 (3H, m), 7.68 (2H, m) and 8.10 (2H, m).

Reactions of (2-alkylaryl)azosulfides with bases

The experiments were performed under argon and at room temperature by addition to a magnetically stirred solution of Bu^{t}OK in DMSO (or DBU in MeCN) (20 mmol in 20 ml) of a solution of azosulfide (2 mmol in 12 ml) in the same solvent. Reactions were kept under magnetic stirring for the time reported in the

text (Table 1 and eqns 1-3), the end of process being judged following by tlc the disappearance of substrate. Usual work-up involved pouring of the reaction mixture into ice/3% HCl followed by extraction with ether, washing of the combined extracts with brine, drying (Na_2SO_4) and rotoevaporation of the solvent under reduced pressure. Column chromatography of the residue on silica gel (eluants: petroleum ether and gradients with CH_2Cl_2 or AcOEt) allowed separation of the products. The structure of all the indazoles herein has been confirmed by ^1H nmr analysis.

Indazole (**2a**): mp 144.9-145.9 °C (toluene/light petroleum) (lit.:[10a] 143-144 °C).

4-Methylindazole (**2b**): mp 110.2-112.7 °C (H_2O) (lit.:[10a] 112-113 °C).[18]

5-Methylindazole (**2c**): mp 109.0-110.2 °C (light petroleum) (lit.:[10a] 111°C).

6-Methylindazole (**2d**): mp 181.5-183.0 °C (light petroleum) (lit.:[19] 177-178 °C).[18]

5,7-Dimethylindazole (**2e**): mp 131.5-132.5 °C (H_2O) (lit.:[20] 133-134 °C).

5-Methoxyindazole (**2f**): mp 166.6-168.4 °C (H_2O) (lit.:[10a] 167.5-168.5 °C).[18]

5-Chloroindazole (**2g**): mp 115.1-116.7 °C (light petroleum) (lit.:[10a] 116-117 °C).[18]

6-Chloroindazole (**2h**): mp 176.7-177.6 °C (H_2O) (lit.:[10a] 174-175 °C).[18]

7-Chloroindazole (**2i**): mp 130.8-132.3 °C (light petroleum) (lit.:[21] 134-136 °C).[18]

5-Bromoindazole (**2j**): mp 130.0-130.7 °C (light petroleum) (lit.:[22] 132-133 °C).[18]

5-Bromo-7-methylindazole (**2k**): mp 185.7-186.7 °C (toluene/light petroleum); ^1H nmr: δ 2.55 (3H, s), 7.28 (1H, m), 7.75 (1H, m) and 8.02 (1H, br s).[18] *Anal.* Calcd for $C_8H_7N_2Br$: C, 45.53; H, 3.34; N, 13.27%. Found: C, 44.89; H, 3.25; N, 13.11%.

3-Methylindazole (**2l**): mp 111.2-113.0 °C (H_2O) (lit.:[10a] 110-111 °C).

3-Ethylindazole (**2m**): mp 71.8-72.9 °C (H_2O) (lit.:[7] 74-75 °C).

3-Vinylindazole (**2n**): mp 115.5-116.5 °C (light petroleum) (lit.:[12a] 117.5-118.5 °C).

5-Nitroindazole (**2o**): mp 207.0-208.2 °C (lit.:[10a] 208-209 °C).

6-Nitroindazole (**2p**): mp 179.3-179.9 °C (toluene) (lit.:[10a] 179-180 °C).

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