Novel Thermal Rearrangement of Fused Diaryl-*v*-Triazolium Salts to Neutral Indazole Derivatives. Fused Azolium Salts. 16[†]

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Alkylation of 1,3-diaryl-*v*-triazolo[1,5-*a*]benzimidazole (**1**) by trimethyloxonium salt afforded selectively the 4-methyl quaternary salt **2**, whereas reaction with dimethyl sulfate at elevated temperature resulted in ring transformation, implying ring opening to a nitrenium cation and a subsequent electrophilic ring closure to give a benzimidazolylindazole product **5**. Independent of the methylation, a similar easy thermal rearrangement was observed with alkylated 1,3-diaryl-*v*-triazolo[1,5-*a*]benzimidazolium (**2** → **4**) and the related benzothiazolium salt (**7** → **8**). Extension of the reaction to diaryl-*v*-triazolopyridinium salt (**9** → **10** + **11**) allowed observation of an additional novel reaction path that provided further support for the supposed reaction mechanism.

As a continuation of a series of alkylation experiments on fused azoles,[1] we decided to study the selectivity of methylation of the 6 + 5 + 5 fused *v*-triazolobenzimidazole ring system.[2] The 1-(*p*-bromophenyl)-3-phenyl-substituted compound **1** when reacted with trimethyloxonium fluoroborate afforded one single product under mild conditions (room temperature), the structure of which proved to be unambiguously (NOE experiments) the 4-methyl-substituted salt **2** (Scheme 1). This observation seemed to be in accordance with the expectations for two reasons: (i) we have carried out semiempirical quantum chemical calculations (Table 1) for **1** and found that the lone pair density (called "n_{HOMO}" by us and proved to be of diagnostic importance for assumption of the site of alkylation of heteroaromatic systems[3]) of N-4 was significantly higher than that of the alternative position N-2; (ii) N-4 is sterically less hindered than N-2.

When the tricyclic compound **1** was, however, alkylated by dimethyl sulfate at 100 °C, a totally different product was isolated from the reaction mixture, which proved to be 1,3-dimethyl-2-(1-arylindazol-3-yl)benzimidazolium salt (**5**). A possible rationalization of this dramatic structural change is to assume that the same methylation reaction as above takes place first to give **2**, which undergoes valence bond isomerization under the forced reaction conditions (100 °C) to the nitrenium cation **3**. This reactive species, however, cannot only afford **2** through the equilibrium but can also undergo an intramolecular electrophilic aromatic substitution on the phenyl substituent to give **4**, and this proposed neutral intermediate gives under the alkylating conditions the dimethyl salt **5**.

This mechanistic picture implies that the observed ring transformation of **2** should take place independently from the second alkylation step and is induced by the higher temperature rather than by the alkylating reagent. This consideration was nicely supported by heating **2** in dichlorobenzene to lead to the previously suggested intermediate **4**, which was now isolated in crystalline form.

Scheme 1

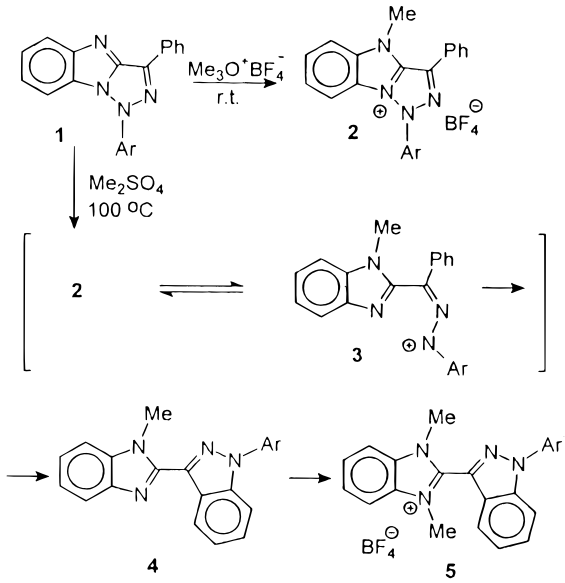

Table 1. HOMO and n_{HOMO} densities of N-2 and N-4 of *v*-Triazolobenzimidazole[a]

atom	c^2_{HOMO}	$c^2_{n_{HOMO}}$
N-2	0.023	0.017
N-4	0.133	0.421

[a] AM1 calculations, 154 iterations.

Another consequence of the above mechanism is that any cation related to **2** should show the same reactivity and, thus, the imidazole-methyl group could be, in principle, replaced even by a hydrogen atom. Thus, the above ring transformation could also be expected with a simple acidic treatment of the neutral compound **1**.

We checked this possibility by heating **1** in trifluoroacetic acid under reflux conditions and found that the expected rearrangement was completed in 4 h and the benzimidazolylindazole derivative **6** was formed as a crystalline product in good yield (90%) (Scheme 2). No reaction was found, however, with heat treatment of **1** in neutral organic solvent (dimethyl formamide, 100 °C, 3 days), which supports the above mechanism and reveals

[†] Part 15: Kotschy, A.; Hajós, Gy.; Messmer, A.; Jones, G. *Tetrahedron* **1996**, *52*, 1399. Part 14: Bátori, S.; Messmer, A. *J. Heterocycl. Chem.* **1994**, *31*, 1641.

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(1) (a) Messmer, A.; Hajós, Gy.; Juhász-Riedl, Zs.; Sohár, P. *J. Org. Chem.* **1988**, *53*, 973. (b) Juhász-Riedl, Zs.; Hajós, Gy.; Gács-Baitz, E.; Kollenz, G.; Messmer, A. *Chem. Ber.* **1991**, *124*, 1477.

(2) Messmer, A.; Gelléri, A. *Angew. Chem.* **1967**, *72*, 792.

(3) Timári, G.; Hajós, Gy.; Bátori, S.; Messmer, A. *Chem. Ber.* **1992**, *125*, 929.

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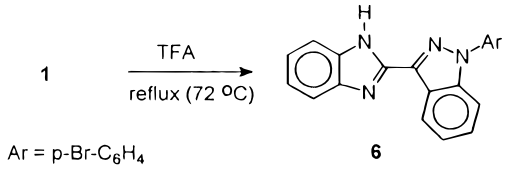
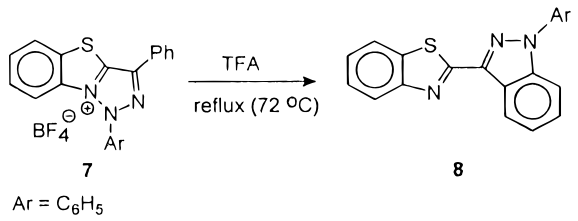
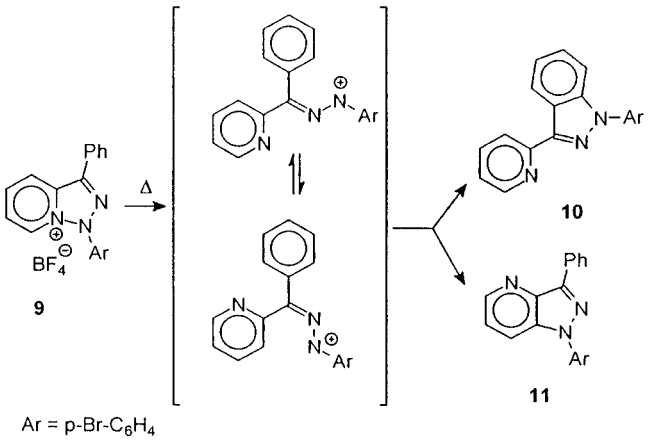
Scheme 2



Scheme 3



Scheme 4



that formation of a cation related to **2** is necessary to the success of the process. It is interesting to note, furthermore, that also the ring transformation of the methylated salt **2** proceeds in trifluoroacetic acid much smoother than in aprotic solvents (*e.g.*, dichlorobenzene). This may be due to the strong protonation of the benzimidazole moiety, which hinders the reverse reaction of **3** to **2** and thereby enhances the chance of the irreversible formation of **4**.

The key step of the observed ring transformation is the valence bond isomerization of **2** to **3**. Such isomerization with neutral *v*-triazoles is well known and widely documented in the literature: numerous examples are known in the cases of monocyclic triazoles (*e.g.*, Dimroth rearrangement)[4] and also with neutral fused triazoles.[4,5] To the best of our knowledge, however, this is the first case where a ring opening of a *v*-triazolium cation was observed.

We have also found that this new ring transformation can be extended to additional related ring systems. Two such cases have been investigated.

(a) The tricyclic 1-aryl-3-phenyl-*v*-triazolo[5,1-*b*]benzothiazolium salt **7**[2] was heated in TFA and afforded, for a more prolonged reaction time compared to the above case, the indazolyl compound **8** in good yield (Scheme 3).

(b) In contrast to the previously mentioned tricyclic compounds of 6 + 5 + 5 fusion pattern, the bicyclic *v*-triazolopyridinium salt (6 + 5 fusion) was also subjected to ring transformation experiments. This model compound differs from the above cases both in the fusion type and in the structural feature that there are two alternative targets for the electrophilic attack of the nitrenium cation: (i) the phenyl substituent, *i.e.*, the same as above, and (ii) the β-carbon atom of the pyridine ring.

We found that the bicyclic salt **9** reacted slowly, and extremely forced conditions were needed (180 °C in dichlorobenzene) in order to observe any transformation. The starting compound disappeared within 3 days and afforded a main component (58%) accompanied by a byproduct (4%), which was separated by column chromatography. According to the above expectations, the two compounds were found to be the products of the two types of the nitrenium cation attacks: the pyridylindazole compound **10**, which was formed in the majority of reactions, corresponds to the same type of product as found with the above tricyclic cases, whereas the second (*i.e.*, minor) component was the pyrazolo[4,3-*b*]pyridine derivative **11**, which is the result of the electrophilic substitution of the nitrenium cation on the far less reactive pyridine ring (Scheme 4). Simultaneous formation of **10** and **11** provides convincing support for the intermediate formation of the supposed nitrenium cation.

A thorough investigation of the observed ring transformation and studies on the scope and limitation of this reaction are in progress.

Experimental Section

1-(4-Bromophenyl)-3-phenyl-*v*-triazolo[1,5-*a*]benzimidazole (1). This compound was prepared according to the synthesis of the 1,3-diphenyl derivative described in our earlier paper:[2] To a solution of 2-benzoylbenzimidazole 4-bromophenylhydrazone[6] (1.17 g, 3 mmol) in dichloromethane (30 mL) was added a solution of *N*-bromosuccinicimide (0.62 g, 3.5 mmol) in dichloromethane (30 mL) dropwise at 0 °C. The stirring was continued overnight at room temperature. Ether (10 mL) was then added, and the precipitate was filtered off. The white crystals were suspended in 10% NaOH (20 mL) and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, and solvent was removed under reduced pressure. Crystallization from ethanol−chloroform (5:2) afforded **1** as a white solid: yield 73%; mp 205 °C dec; IR (KBr) 2984, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 1H), 7.49 (m, 1H), 7.50 (m, 1H), 7.51 (m, 1H), 7.57 (m, 1H), 7.58 (d, 2H), 7.72 (d, 2H), 8.01 (d, 1H), 8.48 (m, 2H). Anal. Calcd for $C_{20}H_{13}N_4Br$: C, 61.71; H, 3.37; N, 14.39. Found: C, 61.81; H, 3.23; N, 14.46.

1-(4-Bromophenyl)-4-methyl-3-phenyl-*v*-triazolo[1,5-*a*]-benzimidazolium Fluoroborate (2). To a solution of **1** (1.00 g, 2.6 mmol) in 40 mL of dry dichloromethane was added 0.6 g (4 mmol) of trimethyloxonium fluoroborate at room temperature. Stirring was continued for 1 day. The reaction mixture was evaporated to half of its volume under reduced pressure. Ether (30 mL) was added, and the white precipitate was filtered off. Repeated precipitation gave 0.9 g (71%) of **2**: mp 184 °C dec; IR (KBr) 1589, 1496, 1451, 1074, 1054,744 cm^{-1}; ^1H NMR (CD_3CN) δ 4.07 (s, 3H), 7.59 (ddd, 1H), 7.68 (t, 1H), 7.7 (m, 3H), 7.82 (d, 2H), 7.87 (ddd, 1H), 7.89−7.92 (m, 2H), 7.97 (m, 1H), 7.97 (m, 2H). Anal. Calcd for $C_{21}H_{16}N_4Br$: C, 51.36; H, 3.28; N, 11.41. Found: C, 51.41; H, 3.20; N, 11.47.

2-(1-(4-Bromophenyl)indazol-3-yl)-1,3-dimethyl-benzimidazolium Fluoroborate (5). A mixture of **1** (1.00 g, 2.6 mmol) and 6 mL of dimethyl sulfate was heated at 100 °C for 3 days. The excess of dimethyl sulfate was removed under reduced pressure. Water (30 mL) was then added, and the precipitate was filtered off. The white crystals were suspended

(4) For reviews, see: (a) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33. (b) Jones, G.; Sliskovic, R. *Adv. Heterocycl. Chem.* **1983**, *34*, 79. (c) Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, *79*, 181

(5) Davies, L. S.; Jones, G. *J. Chem. Soc. C.* **1971**, 759.

(6) Obtained as a yellow solid (mp 215 °C) according to a routine literature procedure: Bystricky, L.; Przeworsky, M. *Chem. Ber.* **1915**, *45*, 3499.

in 10 mL of acetonitrile, and 10 mL of 10% HBF_4 was added, whereupon a clear solution was formed from which the fluoroborate salt precipitated (0.4 g, 31%): mp 280−281 °C; IR (KBr) 3531, 1524, 1490 cm^{-1}; ^1H NMR (CD_3CN) δ 4.10 (s, 6H), 7.55 (ddd, 1H), 7.72 ddd, 1H), 7.80 (dd, 2H), 7.81 (d, 2H), 7.86 (d, 2H), 7.90 (dt, 1H), 7.97 (dd, 2H), 8.00 (m, 1H). Anal. Calcd for $C_{22}H_{16}N_4BrBF_4$: C, 52.29; H, 3.56; N, 11.09. Found: C, 52.14; H, 3.81; N, 10.77.

General Procedure for Transformation of Fused Triazolium Salts into Indazole Derivatives. A solution of 1 mmol of starting material in TFA was heated at reflux (72 °C) for a sufficient period (TLC) . The solvent was removed under reduced pressure. The resulting reaction mixture was suspended with 10 mL of 10% NaOH and extracted with chloroform. The organic layer was evaporated to dryness, and the residue was purified by column chromatography (silica/$CHCl_3$). Analytical samples were obtained by recrystallization from ethanol.

3-(Benzimidazol-2-yl)-1-(4-bromophenyl)indazole (6). According to the general procedure, refluxing **1** in TFA for 4 h gave **6** as a white solid: yield 90%; mp 255−256 °C; IR (KBr) 3049, 2641, 1488 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (m, 2H), 7.43 (ddd, 1H), 7.53 (dd, 1H), 7.54 (ddd, 1H), 7.70 (m, 4H), 7.73 (d, 1H), 7.93 (td, 1H), 8.79 (dt, 1H), 10.10 (s, 1H). Anal. Calcd for $C_{20}H_{13}N_4Br$: C, 61.71; H, 3.37; N, 14.39. Found: C, 61.63; H, 3.22; N, 14.33.

1-(4-Bromophenyl)-3-(1-methylbenzimidazol-2-yl)indazole (4). According to the general procedure, refluxing **2** in TFA for 4 h gave **4** as a white solid: yield 89%; mp 184−185 °C; ^1H NMR ($CDCl_3$) δ 4.33 (s, 3H), 7.42 (m, 2H), 7.46 (td, 1H), 7.51 (m, 1H), 7.56 (ddd, 1H), 7.72 (m, 4H), 7.76 (d, 1H), 8.07 (m, 1H), 8.85 (d, 1H). Anal. Calcd for $C_{21}H_{15}N_4Br$: C, 62.54; H, 3.75; N, 13.89. Found: C, 62.60; H, 3.48; N, 13.91.

3-(Benzothiazol-2-yl)-1-phenylindazole (8). According to the general procedure, refluxing **7** in TFA for 50 h gave **8** as a white solid: yield 86%; mp 153 °C; ^1H NMR ($CDCl_3$) δ 7.40−7.46 (m, 3H), 7.52 (m, 2H), 7.60 (m, 2H), 7.78 (d, 1H), 7.82 (m, 2H), 7.96 (dd, 1H), 8.17 (dd, 1H), 8.77 (td, 1H). Anal. Calcd for $C_{20}H_{13}N_3S$: C, 73.37; H, 4.00; N, 12.83. Found: C, 73.00; H, 3.84; N, 12.78.

Transformation of 1,3-Diaryl-*v*-triazolo[1,5-*a*]pyridinium Fluoroborate (9) in Dichlorobenzene. 3-(4-Bromophenyl)-1-phenyl-*v*-triazolo[1,5-*a*]pyridinium fluoroborate (**9**)[7] (1.50 g, 3.7 mmol) in 30 mL of dichlorobenzene was refluxed (180 °C) for 70 h. The solvent was removed under reduced pressure. The residue was suspended with 10 mL of 10% NaOH and extracted with chloroform. The organic phase was dried over $MgSO_4$, evaporated to dryness, and subjected to column chromatography (silica). Elution with chloroform allowed the separation of **10** and **11**.

1-(4-Bromophenyl)-3-(pyrid-2-yl)indazole (10): yield 0.7 g (58%) (white needles, EtOH); mp 127 °C; ^1H NMR ($CDCl_3$) δ 7.30 (ddd, 1H), 7.36 (ddd, 1H), 7.49 (ddd, 1H), 7.69−7.72 (m, 4H), 7.73 (m, 1H), 7.80 (dt, 1H), 8.27 (d, 1H), 8.76 (d, 1H), 8.78 (m, 1H). Anal. Calcd for $C_{18}H_{12}N_3Br$: C, 61.73; H, 3.45; N, 12.00. Found: C, 61.82; H, 3.43; N, 11.95.

1-(4-Bromophenyl)-3-phenylpyrazolo[4,3-*b*]pyridine (11): 52 mg (4%); ^1H NMR ($CDCl_3$) δ 7.39 (dd, 1H), 7.44 (m, 1H), 7.54 (m, 2H), 7.70 (s, 4H), 8.06 (dd, 2H), 8.58 (m, 2H), 8.74 (dd, 1H); MS *m*/*z* (rel int) 349 (100, M^+), 269 (26), 167 (13).

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(7) Synthesized according to the literature procedure and transformed to a fluoroborate salt by adding 50% hydrogen fluoroborate to the hot aqueous solution of the bromide salt: Kuhn, R.; Münzing, W. *Chem. Ber.* **1953**, *86*, 858. Experimental data: yield 80%; mp 225−226 °C; IR (KBr) 1489, 1127, 1073, 1027, 836, 785 cm^{-1}; ^1H NMR (CD_3CN) δ 7.71 (m, 3H), 7.78 (d, 2H), 7.94 (dt, 1H), 8.01 (d, 2H), 8.07 (m, 2H), 8.27 (ddd, 1H), 8.71 (dt, 1H), 9.00 (dd, 1H). Anal. Calcd for $C_{18}H_{13}N_3BrBF_4$: C, 49.36; H, 2.99; N, 9.59. Found: C, 49.26; H, 2.87; N, 9.62.