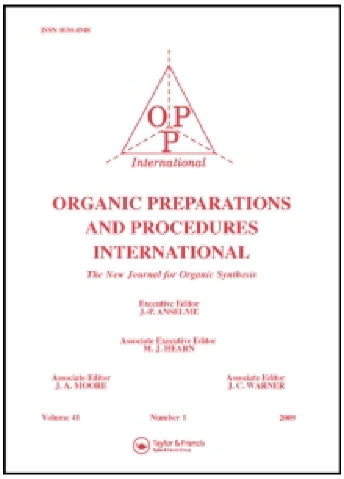

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ISOMER DISTRIBUTION IN THE METHYLATION OF [1]-BENZOTHIENO[2,3-d]TRIAZOLE UNDER PHASE-TRANSFER CATALYTIC CONDITIONS

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ISOMER DISTRIBUTION IN THE METHYLATION OF [1]-BENZOTHIENO[2,3-d]TRIAZOLE UNDER PHASE-TRANSFER CATALYTIC CONDITIONS

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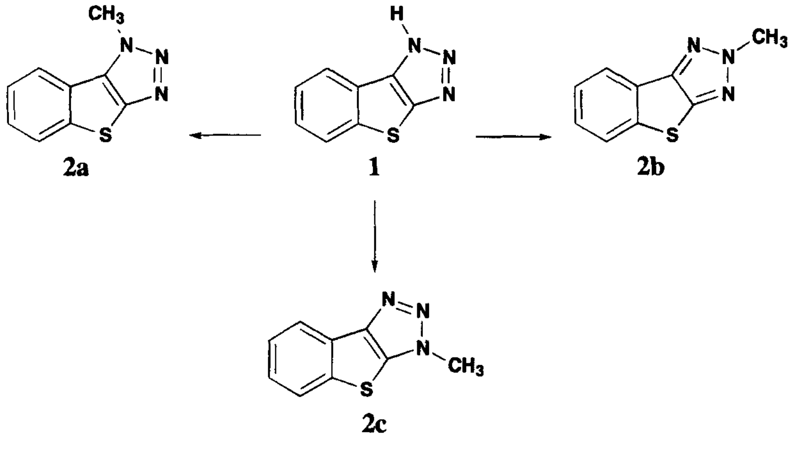
We have been interested in specific regioselectivity effects of the nature of the phase-transfer catalyst (PTC) on the course of various reactions. As a continuation of our investigations on the alkylation of ambident anions,[1] under phase-transfer catalysis, we devoted our attention to the N-alkylation of the title compound **1**. The synthesis of **1** and of its N-methylated products (**2a-2c**) as well



as the respective spectroscopic data have already been described in the literature,[2,3] but the structural assignments are partially incorrect.

Guerrera and coworkers obtained varying mixtures of species **2a**-**2c**[3] in their study of the influence of the nature of the reagent on N-alkylation selectivity. The authors ventured to assign structures on the basis of spectral data (mass spectra, ^1H NMR, ^{13}C NMR, using also NOE experiments). Compound **2b** (mp. 52-53°) was identified unequivocally on the basis of mass spectral and NMR evidence. The other two compounds (mp. 132-133° and 96-97°) have very similar MS, ^1H and ^{13}C NMR data, but NOE experiments seemed to indicate that the higher melting compound is **2c**. A single crystal X-ray structural analysis[4] indicated clearly that this compound is in reality **2a**. Thus, the structures of **2a** and **2c** as given by Guerrera *et al.* should be reversed.

TABLE 1. Isomer Distribution for the N-methylation of **1** with Dimethyl Sulfate[a]

No.	Catalyst	**2a** (%)	**2b** (%)	**2c** (%)	Conversion (%)
1	None	24	12	64	94
2	[$((Me_2N)_3P)_2$ =N] Cl	9	53	38	89
3	Me_4N Br	19	20	61	89
4	18-crown-6	7	56	37	80
5	Ph_4As Br	8	57	35	98
6	TEBA Br	19	46	35	95
7	Bu_4N Br	10	43	47	94
8	Oct_4N Br	10	42	48	96
9	Benzo-15-crown-5	12	31	57	92
10	Dibenzo-18-crown-6	8	45	47	89

a) Standard conditions : 5 mmol of **1**, 5,5 mmol of Me_2SO_4, 6 mL of 50% NaOH, 20 mL of toluene, 1mmol of catalyst, 1 hr reflux.

The main point of our investigation was whether there would be a directing influence on the **2a**-**2c** isomer distribution by the nature of the cation of the phase-transfer catalyst. The results of the Italian workers, suggested dimethyl sulfate to be the most suitable reagent. Our experiments gave **2a**-**2c** mixtures as reported in Table 1. Analysis was performed by gas chromatography. It became evident that the reaction time can be shortened dramatically under PTC in comparison to conditions used by Guerrera *et al.* (24 hrs vs. 1 hr!).[3] As might have been expected from the results of the Italian authors, methyl iodide gave always about 90% of **2b** in our hands, no matter which catalyst was used. Our results from other PTC reactions of ambident ions[1] allowed the classification of catalysts into three groups, two of which [(a) and (b)] have relatively strong directing effects on the course of reactions:

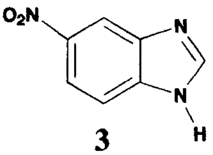
(a) Small, hard ammonium ions of the type $RNMe_3^+$ and certain crown ethers, particularly benzo-15-crown-5.

(b) Large, sterically shielded and highly delocalized cations, such as tetraphenylarsonium and phosphiminium salts such as [$Ph_3P{=}N{=}PPh_3$] Cl and "Schwesinger" salts,[5] such as P [$N{=}P(NMe_2)_3$]$_4$X and [$(Me_2N)_3P{=}N{=}P(NMe_2)_3$] X.

(c) Typical phase transfer catalysts such as TEBA and tetrabutylammonium salts which exhibit little directing action towards competing reaction paths.

The same effects of catalysts have been observed in some other reactions, *e.g.* the **chemoselectivities** of halide exchange in dihalocarbenes [6] and competitive reactions of the species dihalocarbene and trihalomethyl anion [7].

Inspection of the data of Table 1 shows that the catalysts influences the regiochemistry of alkylation, but very little. The small differences in nucleophilicity of the three nitrogen sites in the anion of **1** are modified to a certain extent by the nature of the catalyst ion. As can be seen in the Table, catalysts of group (a) bring about the formation of relatively more **2c** (Experiments 3, 9) whereas catalysts of group (b) favor **2b** (Experiments 2, 4, 5), while those of group (c) are intermediate. The largest proportion of **2a** (24%) is formed in the non-catalyzed process. It is interesting to note that there are no catalyst influences the site of methylation in the polar bicyclic heterocycle 5(6)-nitrobenzimidazole (**3**), whereas the related compound 4(5)-nitroimidazole (**4**) exhibited effects similar in magnitude to the ones observed in the present study.[1d]



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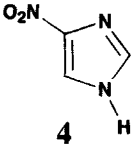

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EXPERIMENTAL SECTION

General Method for the Alkylations of 1 with Dimethyl Sulfate.- A mixture of 1 (5 mmol) and dimethyl sulfate (5,5 mmol), 6 mL of 50% NaOH and 1 mmol of catalyst in 20 mL of toluene was refluxed for one hour. After cooling to room temperature, water was added to the mixture and the aqueous solution was extracted with toluene three times. The organic layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure to give a residue containing nearly 100% of methylated products. Column chromatography of this residue on silica gel [petroleum ether:ether (5:1)] gave the fast-moving isomer **2b** (mp. 52-53°) and a mixture of **2a** (mp. 132-133°) and **2c** (mp. 96-97°). These compounds were further separated by repeated chromatography under the conditions described above. The spectroscopic data were identical to the ones reported in ref. 3 (except for the structural reassignment of **2a** and **2c**). All these compounds are colorless solids.

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