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# Reactions of Bunte salts with carbocations of isobenzofuranone and isoindolone

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ABSTRACT

A convenient method for the preparation of functionalized derivatives of isobenzofuran-1(3*H*)-ones and isoindol-1(3*H*)-ones by reactions of their carbocations with Bunte salts is described. The reactions proceed by means of electrophilic attack on the S(II)-atom of the Bunte salts.



Bunte salts (organic S-substituted thiosulfates)[1] are interesting as reagents for introducing sulfur-containing groups, particularly by reactions with different C-electrophiles. The only known example of such reactions is the carbamoylmethylthiolation of a benzhydryl carbocation using sodium carbamoylmethyl thiosulfate (**1a**)[2] in which atom S(II) plays the role of nucleophilic center. The reaction is accompanied by hydrolytic cleavage of the S–S bond and S-desulfonation, giving an almost quantitative yield of 2-benzhydrylthioacetamide, the key intermediate in a new synthetic approach to the nootropic drug 'modafinil' (2-benzhydrylsulfinylacetamide).[3]

Application of this approach to other carbocations and Bunte salts is of considerable synthetic interest, in particular, for the synthesis of new bioactive compounds. Due to the weak nucleophilic character of Bunte salts, only highly active carbocations, for example, 3-oxo-1,3-dihydroisobenzofuran-1-yliums (**2**) and their isoindole analogs, 3-oxo-1,3-dihydroisoindol-1-ylium cations (**3**), are the most promising for these reactions. Cation **2a** (Scheme 1) is generated by dissolving 3-hydroxyisobenzofuran-1(3*H*)-one (**4a**) (the cyclic form of *o*-formylbenzoic acid) in concentrated $H_2SO_4$. This cation, for example, readily reacts with arenes, such as benzene, giving products of electrophilic aromatic substitution.[4] It can be assumed that cations **3** are generated from 3-oxo-1,3-dihydroisobenzofuran-1-yl acetates **5** in a strong acidic medium ($CF_3COOH$) and are responsible for electrophilic reactions of these compounds (Scheme 2).

In this work we present a new method for the synthesis of functionalized 3-(alkylsulfanyl)isobenzofuran-1(3*H*)-ones **6** and 3-(alkylsulfanyl)isoindol-1(3*H*)-ones **7** from the precursors of cations **2** and **3** by means of reactions with functionalized Bunte salts **1a–e** in acidic medium. Compounds of this type are useful for the preparation of quinones,[5,6] including naturally occurring examples, via the Hauser–Kraus reaction,[7,8] and glucokinase inhibitors as potential antidiabetic drugs.[9] The common route to such compounds is via nucleophilic alkylation of isobenzofuran-1(3*H*)-one and isoindol-1(3*H*)-one 3-mercapto derivatives, or by heterocyclization of Schiff bases derived from ethyl 2-formylbenzoate and alkyl 2-mercaptoacetates.[10,11] We found that compound **4a**, the precursor of cation **2a**, reacts smoothly with thiosulfate **1a** in concentrated $H_2SO_4$ at room temperature to give 3-carbamoylmethylthio derivative **6a** (yield 77%), the structure of which was established by X-ray analysis (Fig. 1).[12] The most important bond lengths are as follows: S(1)–C(9) 1.812(1), S(1)–C(8) 1.800(1), C(1)=O(2) 1.207(1), C(1)–O(1) 1.363, C(8)–O(1) 1.462(1), C(10)=O(3) 1.238(1), C(10)–N(1) 1.330(1) Å. These parameters do not differ from standard values.

The 6,7-dimethoxy derivative **4b**, a cyclic form of opianic acid, gave 6,7-dimethoxy-3-carbamoylmethylthio-isobenzofuran-1(3*H*)-one (**6b**) following a similar reaction (Scheme 1).

2-Aryl-3-acetoxyisoindol-1(3*H*)-ones **5a**,**b** and 2-cyanoacetylamino-3-acetoxyisoindol-1(3*H*)-one **5c** were also active as carbocation precursors in reactions with Bunte salts. Generally, these reactions were conveniently carried out in $CF_3COOH$ either at room temperature or under moderate heating (Scheme 2, Table 1). Under these conditions the Bunte salts were stable to $CF_3COOH$.

Bunte acids containing an amino group as part of a pharmacophoric dialkylaminoalkyl substituent, can also be used as effective S-nucleophiles, because the amino group exists as the inactive protonated form.

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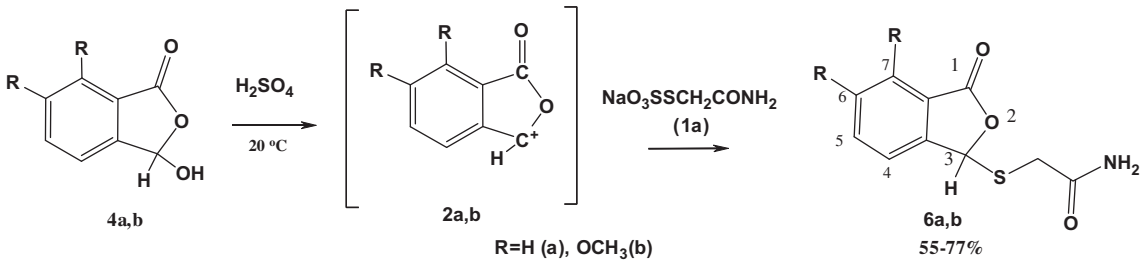
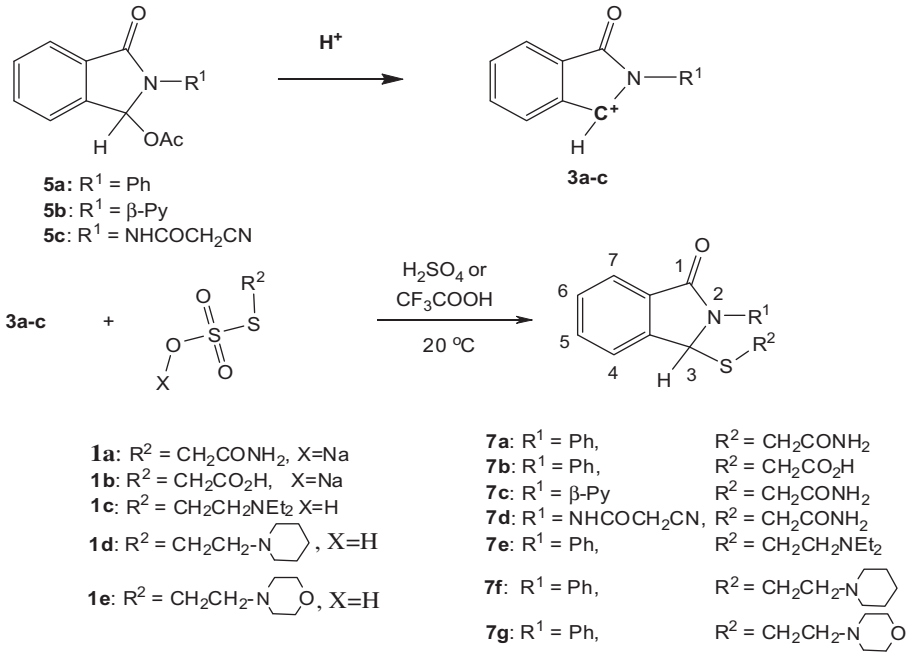



**Scheme 1.** Reactions of the Bunte salt **1a** with isobenzofuranone carbocations.




**Scheme 2.** Reactions of the Bunte salts **1a–e** with isoindolone carbocations.

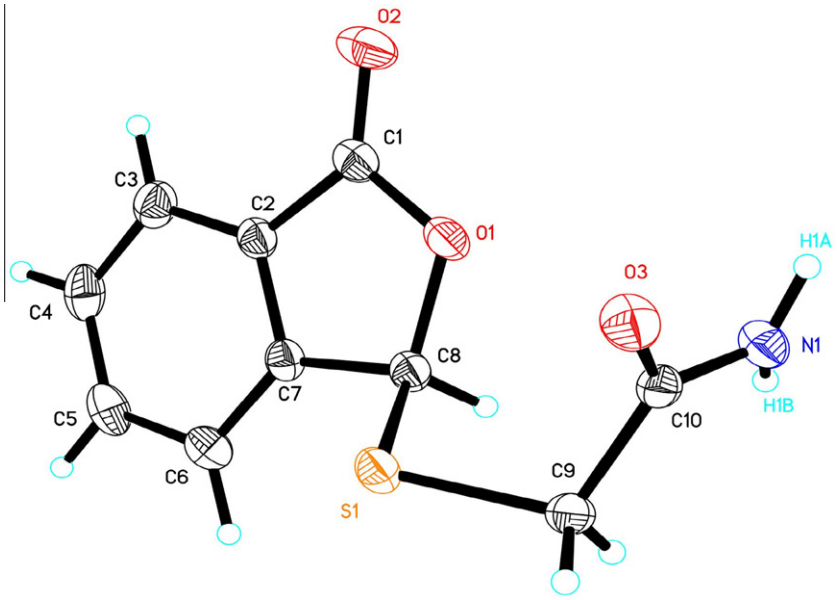
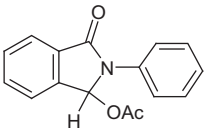
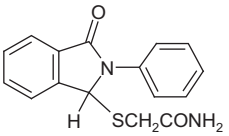
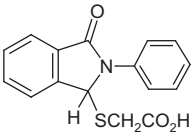
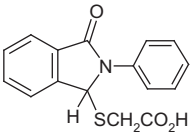
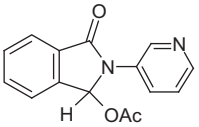
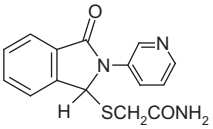
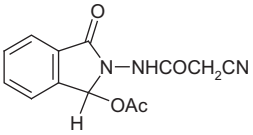
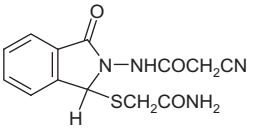
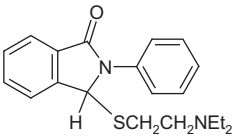
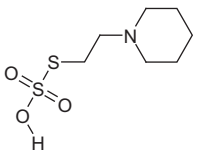
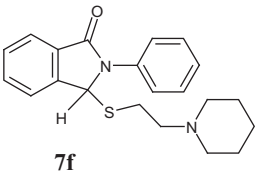
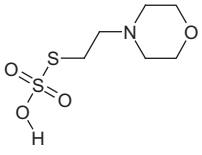
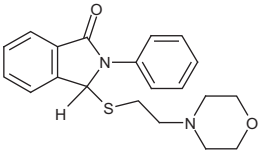



**Figure 1.** A SHELXTL-Plus drawing of the molecular structure of **6a**. Thermal ellipsoids are shown at the 50% probability level.

**Table 1**
Yields of compounds **7a–g** obtained by reaction of isoindolones **5a–c** and Bunte salts **1a**,**b** or Bunte acids **1c–e**[13]

| Entry | Acid | Bunte salt (acid) | 3-Acetoxyisoindolone | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | $H_2SO_4$ | $NH_2COCH_2SSO_3Na$ **1a** |  **5a** |  **7a** | 80 |
| 2 | $H_2SO_4$ | $HO_2CCH_2SSO_3Na$ **1b** | **5a** |  **7b** | 67 |
| 3 | TFA | **1b** | **5a** |  **7b** | 86 |
| 4 | TFA | **1a** |  **5b** |  **7c** | 77 |
| 5 | TFA | **1a** |  **5c** |  **7d** | 49 |
| 6 | TFA | $HSO_3SCH_2CH_2NEt_2$ **1c** | **5a** |  **7e** | 40 |
| 7 | TFA |  **1d** | **5a** |  **7f** | 48 |
| 8 | TFA |  **1e** | **5a** |  **7g** | 53 |

The structures of compounds **7** were established by mass spectrometry and 1D, 2D $^1H$, $^{13}C$ and $^{15}N$ NMR spectroscopy.

In summary, we have developed a new approach to the synthesis of isobenzofuran-1(3*H*)-ones and isoindol-1(3*H*)-ones bearing 3-alkylthio groups. The synthetic strategy used is based on the nucleophilic properties of Bunte salts which enable their efficient interaction with reactive carbocationic electrophiles. It is important to note that Bunte salts, according to our preliminary data, are also active toward strongly electrophilic organic halides such as α-haloketones, for which the $S_N2$ mechanism is characteristic Table 1.

*General procedure for the synthesis of isobenzofuranones* **6**. The appropriate *o*-formylbenzoic acid (3.3 mmol) was titrated with concentrated $H_2SO_4$ (2 mL) until dissolution and then with thiosulfate **1a** (0.7 g, 3.6 mmol). The mixture was left for 12 h at rt and then treated with cold $H_2O$ (25 mL). The solid product was filtered, washed with $H_2O$, and dried.

Compound **6a**: yield 0.57 g (77%), colorless crystals, mp 182–183 °C (MeCN).

$^1H$ NMR (300 MHz, DMSO-$d_6$), $\delta$: 3.25 (d, 1H, $CH_2$, $J$ = 14.4 Hz), 3.37 (d, 1H, $CH_2$, $J$ = 14.4 Hz), 6.97 (s, 1H, CH), 7.01 (s, 1H, $NH_2$),

7.44 (s, 1H, $NH_2$), 7.62 (t, 1H, H(6), $J$ = 7.3 Hz), 7.66 (d, 1H, H(4), $J$ = 7.9 Hz), 7.79 (td, 1H, H(5), $J$ = 7.5 Hz), 7.84 (d, 1H, H(7), $J$ = 7.6 Hz) ppm; IR (neat): $\nu_{max}$ = 3400, 3340, 3304, 3250, 3201(NH), 1754, 1665 (CO), 1599 (aromatic C=C), 1060, 933 $cm^{-1}$ (C–O–C). Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.66; N, 6.27; S, 14.36. Found: C, 53.86; H, 4.85; N, 6.64; S, 14.02; MS (EI, 70 eV): $m/z$ = 165 (M-$CH_2CONH_2$), 133 (M−$SCH_2CONH_2$); the product did not produce a stable molecular ion.

*General procedure for the synthesis of isoindolones* **7**. To a solution of appropriate 3-acetoxyisoindolone **5** (1 mmol) in concentrated $H_2SO_4$ (2 ml) or TFA (1 mL), thiosulfate **1** (1.0–1.1 mmol) was added and the mixture triturated until dissolution of the starting compounds. The reaction times and temperatures were as follows: **7a**—1 h (20–25 °C); **7b**—0.5 h (20–25 °C); **7c**,**d**—1 min (at reflux), **7e–g**—3 h (20–25 °C). The isoindolones were precipitated by addition of $Et_2O$ or a mixture of $Et_2O$–*i*PrOH. The products were separated, triturated with concentrated $NH_4OH$ (5 mL) and cooled with ice until they solidified. The solid was filtered, washed with $H_2O$ and dried.

Compound **7a**: colorless crystals, mp 183–185 °C (MeCN). $^1$H NMR (300 MHz, DMSO-$d_6$): 2.53 (d, 1H, $CH_2$, $J$ = 14.2 Hz), 2.66 (d, 1H, $CH_2$, $J$ = 14.2 Hz), 6.74 (s, 1H, C(3)H), 6.88 (s, 1H, $NH_2$), 7.22 (s, 1H, $NH_2$), 7.27 (t, 1H, *p*-H of Ph, $J$ = 7.4 Hz), 7.46 (t, 2H, *m*-H of Ph, $J$ = 7.8 Hz), 7.60–7.80 (m, 4H, C(4)H–C(7)H), 7.81 (d, 2H, *o*-H of Ph, $J$ = 7.5 Hz) ppm; IR (neat): $\nu_{max}$ = 3408, 3288, 3238, 3187 (NH), 1686, 1630 (CO), 1620, 1600, 1494 $cm^{-1}$ (arom.). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.40; S, 10.74. Found: C, 64.23; H, 5.00; N, 9.63; S, 10.68; MS (EI, 70 eV): $m/z$ = 298 ($M^+$), 240 (M−$CH_2CONH_2$), 208 (M-$SCH_2CONH_2$).

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## Supplementary data

Supplementary data (procedures and characterization data for compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.016.

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12. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre: CCDC 816680. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
13. The syntheses of the Bunte salts and acids **1a–c**,**e** are described in Ref. 2 and elsewhere: Haugland, R.; Kang, H., U.S. Patent, Publ. No: 20050250957; *Chem. Abstr*., **2005**, *143*, 9187; Bretschneider, H. *Monatsh. Chem*. **1950**, *81*, 372–384; Klayman, D. L.; Kenny, D.; Silverman, R. B.; Tomaszewski, J. E. *J. Org. Chem*. **1971**, *36*, 3681–3686; Foye, W. O.; Lanzillo, J. J.; Lowe, Y. H.; Kauffman, J. M. *J. Pharm. Sci*. **1975**, *64*, 211–216. Compound **1d** was prepared analogously to **1c**,**e** starting from β-piperidinoethyl chloride and sodium thiosulfate (see Supplementary data for details).