Tetrahedron Letters, Vol. 34, No. 2, pp. 239-242, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

Formation of 1-Bromocarbonylindazoles *via* Cleavage of 4-Bromo *ortho*-Substituted Arylsydnones with HBr

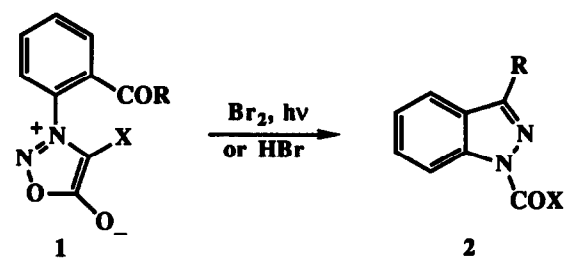
Jeffrey A. Marx and Kenneth Turnbull*

Department of Chemistry, Wright State University, Dayton, Ohio 45435, U.S.A.

Abstract: Treatment of 4-bromo-3-arylsydnones containing an *ortho*-carbonyl substituent (*cf.* **1d-j**) with HBr gas leads to the corresponding, novel 1-bromocarbonyl-3-substituted indazoles (**2d-k**), generally in excellent yield.

For another study we required the bromoacetylsydnone (**1b**). It seemed likely that side-chain bromination of the parent sydnone (**1a**)[1] could be effected using standard conditions (*viz.* bromine / hν[2] or $CuBr_2$[3]). However, in light of the facile bromination of the sydnone 4-position with bromine (*cf.* **1a** to **1d**),[4] to avoid a competitive situation, with consequent product mixtures, it was elected to brominate at the 4-position first and then subject the 4-bromo product (**1d**) to conditions conducive to side-chain bromination. Subsequent formation of **1b** *via* removal of the 4-bromo moiety with Na_2SO_3[5] appeared feasible.

In the event, when 4-bromo-3-(2-acetylphenyl)sydnone (**1d**)[6] was stirred with one equivalent of bromine in CH_2Cl_2 for 1h under sun lamp irradiation (*ca.* 50°C) the product isolated (81%) after rapid, short-path chromatography was the novel 1-bromocarbonylindazole (**2d**) rather than the expected side-chain brominated species (**1c**). We suspected that this unusual reaction was initiated by HBr formed *in situ* and, indeed, treatment of **1d** with HBr gas gave an excellent yield (86%) of the same bromocarbonylindazole **2d**. We have shown now that this latter process is general and efficient by subjecting a series of 4-bromo-3-(2-carbonylaryl)-sydnones (**1e-j**)[6] to HBr treatment. The congeneric 1-bromocarbonylindazoles (**2e-j**) were obtained in each case (except **2j**) in 39-89% yield after rapid, short-path column chromatography (Table 1).



1 **2**

For **2j**, column chromatographic isolation proved problematic due to its existence as the amine salt. It was perceived that basification prior to chromatography would present a potential for polymer formation (undesirable at this time) and, accordingly, in subsequent runs the bromocarbonylindazole amine salt was first converted to the methyl ester amine salt by treatment with methanol then basified with sodium bicarbonate to yield 3-methylamino-1-carbomethoxyindazole (**2k**) in 89% overall yield.

Table 1. Reactions of 3-(2-Carbonyl Containing Aryl)sydnones **1** with HBr

1	R	X	Yield (%) of 2[a]	mp(°C)
a	Me	H	--	--
b	$BrCH_2$	H	--	--
c	$BrCH_2$	Br	--	--
d	Me	Br	86	95-6
e	H	Br	39	76-8
f	Ph	Br	63	95.5-6.5
g	MeO	Br	70	81-2
h	EtO	Br	86	88-90
i	CBr_3	Br	63	160-1
j	MeNH	Br	--	--
k	MeNH	MeO	89	159-60
l	Me	Cl	74	86.5-7
m	Me	MeO	52	62-3
n	Me	EtO	77	32-3

[a]All compounds were fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and combustion analysis

The identities of the relatively stable bromocarbonyl species (**2d-i, k**) were ascertained from their satisfactory spectral (IR, ^{1}H and ^{13}C NMR, mass) and microanalytical data. The main feature of their IR spectra was the characteristic carbonyl absorption at *ca.* 1750 cm^{-1} while the proton NMR spectrum in each case displayed a pattern of two 1H doublets (*ca.* 8.2 δ and *ca.* 7.6 δ) and two 1H triplets (*ca.* 7.5 δ and *ca.* 7.4 δ) in the aromatic region assigned by analogy to other indazoles[7] to the hydrogens at C-4, C-7, C-6 and C-5, respectively. The ^{13}C-NMR spectra also showed similar trends to those reported for simple indazoles[7] and these values are assigned accordingly in Table 2. In addition, chemical evidence supports the structures suggested since treatment of 1-bromocarbonyl-3-methylindazole (**2d**) with methanol or ethanol gave products with the characteristics expected (IR, ^{1}H and ^{13}C NMR, mass) for the corresponding esters **2m** and **2n**, respectively, and hydrolysis of **2d** gave 3-methylindazole in 62% yield.

That the process was not restricted to 4-bromosydnones (*cf.* **1**, X = Br) was demonstrated by subjecting 4-chloro-3-(2-acetylphenyl)sydnone (**1l**)[8] to HCl treatment; 1-chlorocarbonyl-3-methylindazole (**2l**) was obtained in 74% yield. The latter also reacted with water to form 3-methylindazole.

Table 2. ^{13}C NMR Assignments for 1-Bromocarbonylindazoles **2** and Congeners

Compound[a]	C=O	C-7a	C-3	C-6	C-7	C-5	C-4	C-3a
2d	151.6	139.2	138.2	130.0	114.5	125.5	120.5	127.6
2f	152.5	140.4	139.2	130.1	115.0	--[b]	--[b]	130.9
2g	161.2	140.7	138.2	130.9	115.1	125.6	120.3	119.5
2h	160.6	140.5	138.2	130.7	115.1	125.6	120.5	119.8
2i	160.9	141.6	139.3	130.9	114.9	125.8	122.8	121.6
2k	153.8	151.7	141.1	129.6	115.0	123.0	118.8	128.2
2l	151.7	146.4	140.1	130.1	114.9	125.5	120.6	127.4
2m[c]	151.0	149.1	140.4	129.0	114.4	123.5	120.1	125.9
2n	150.4	148.8	140.2	128.8	114.3	123.2	120.0	125.7

[a]run in $CDCl_3$ [b]not assignable [c]run in CD_3COCD_3

The ease of preparation of the requisite bromosydnones (**1d-j**)[6] coupled with the known antiinflammatory and analgesic properties of indazoles such as Bendazac[9] and Benzydamine,[10] respectively, suggest that the present transformation will be of considerable interest. Further studies of its scope and mechanism are underway.

Representative Procedure

Hydrogen bromide gas was bubbled slowly into a stirred solution of 4-bromo-3-(2-acetylphenyl)sydnone (**2d**) [0.052g, 0.182mmol] in dichloromethane (10mL) at room temperature. After 2 minutes the volatiles were removed *in vacuo* to yield a tan solid which, after column chromatography (SiO_2, CH_2Cl_2 as eluant), gave analytically pure 1-bromocarbonyl-3-methylindazole (**2d**) as colourless crystals (0.038g, 86%).

Acknowledgment. Acknowledgement is made to the Midwest Center for Mass Spectrometry (Lincoln, Nebraska) and to D. Bombick (Wright State University) for mass spectrometric data. K. Turnbull thanks Professor Yongren Wu (Beijing Normal University, Beijing, P.R.C.) for technical assistance.

References and Notes

1. Lowe, J.D. and Turnbull, K. *J. Heterocycl. Chem.*, **1986**, *23*, 125.
2. House, H.O. *Modern Synthetic Reactions*, 2nd. Edition, W.A. Benjamin, Inc.: Menlo Park, CA, 1972, p. 460.
3. King, L.C. and Ostrum, K. *J. Org. Chem.*, **1964**, *29*, 3459.
4. Turnbull, K.; Blackburn, T.L. and Esterline, D.T. *J. Heterocycl. Chem.*, **1990**, *27*, 1259.
5. McChord, K.L.; Tullis, S.A. and Turnbull, K. *Synth. Commun.*, **1989**, *19*, 2249.
6. New 4-bromosydnones (*viz.* **2f, h-j**) were prepared using standard conditions[4] and their properties will be reported elsewhere.
7. Elguero, J.; Fruchier, A. and Pardo, M. *Can. J. Chem.*, **1976**, *54*, 1329; Fruchier, A.; Alcade, A. and Elguero, J. *Org. Mag. Res.*, **1977**, *9*, 716; Begtrup, M.; Claramunt, R.M. and Elguero, J. *J. Chem. Soc., Perkin Trans. 2*, **1978**, 99.
8. Prepared by treatment of the parent sydnone **1a** with $KClO_3$ / HCl; Earl, J.C. *Rec. Trav. Chim.*, **1956**, *75*, 1080.
9. Windholz, M., ed. *The Merck Index*, 10th Edition, Merck Inc.: Rahway, NJ, 1983, entry 1033.
10. Windholz, M., ed. *The Merck Index*, 10th Edition, Merck Inc.: Rahway, NJ, 1983, entry 1128.

(Received in USA 24 July 1992; accepted 13 October 1992)