ISSN 1070-4280, Russian Journal of Organic Chemistry, 2007, Vol. 43, No. 4, pp. 635–636. © Pleiades Publishing, Ltd., 2007.
Original Russian Text © I.Z. Kondyukov, Yu.V. Karpychev, P.G. Belyaev, G.Kh. Khisamutdinov, S.I. Valeshnii, S.P. Smirnov, V.P. Il'in, 2007, published in Zhurnal Organicheskoi Khimii, 2007, Vol. 43, No. 4, pp. 636–637.

SHORT COMMUNICATIONS

Sulfur as a New Low-Cost and Selective Reducing Agent for the Transformation of Benzofuroxans into Benzofurazans

I. Z. Kondyukov, Yu. V. Karpychev, P. G. Belyaev, G. Kh. Khisamutdinov, S. I. Valeshnii, S. P. Smirnov, and V. P. Il'in

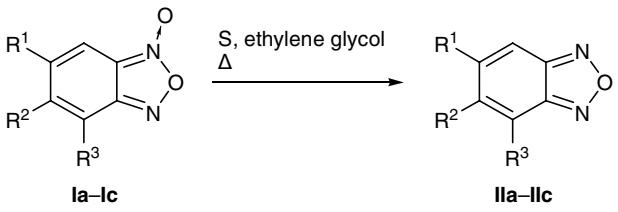
Kristall State Research Institute, ul. Zelenaya 6, Dzerzhinsk, Nizhegorodskaya oblast, 606007 Russia
e-mail: crystall@sinn.ru

Received May 4, 2006; revised August 28, 2006

DOI: 10.1134/S107042800704029X

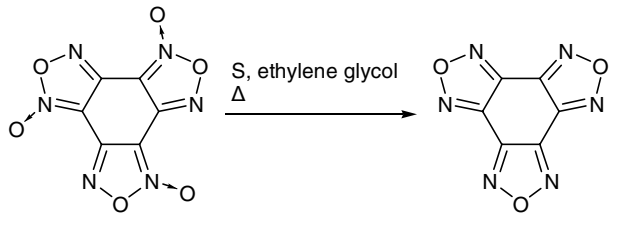
Benzofurazan derivatives exhibit a broad spectrum of biological activity, including antibacterial, antifungal, acaricide, antileukemic, and immunodepressive action [1–3]. An efficient and widely used procedure for the synthesis of these compounds is based on reductive deoxygenation of relatively readily accessible benzofuroxans. Trialkyl- and triarylphosphines, trialkyl phosphites, hydrazine, hydroxylamine, and sodium azide were used as reducing agents in these reactions [4]. However, the above reducing agents are either difficultly accessible or highly toxic, or explosive and are not selective.

We have found a new accessible, safe, and selective reducing agent for the transformation of benzofuroxans into benzofurazans. It is elemental sulfur or its mixture with morpholine. For example, elemental sulfur in ethylene glycol at 150–160°C readily reduced benzofuroxan (**Ia**), 5-nitrobenzofuroxan (**Ib**), and 4,6-dinitrobenzofuroxan (**Ic**) to the corresponding benzofurazans **IIa**–**IIc** in 28–58% yield; analogous reaction with benzotrifuroxan (**III**) at 145–150°C gave 54% of benzotrifurazan (**IV**).



Ia–Ic **IIa–IIc**

$R^1 = R^2 = R^3 = H$ (**a**); $R^1 = R^3 = H$, $R^2 = NO_2$ (**b**); $R^1 = R^3 = NO_2$, $R^2 = H$ (**c**).



III **IV**

When benzofuroxan **Ib** was heated in ethylene glycol for 2 h at 150–160°C in the absence of sulfur, no more than 5% of benzofurazan **IIb** was formed. This result indicates that sulfur acts as reducing agent. Addition of morpholine to the reaction mixture enhances the reactivity of sulfur: the reaction time in the reduction of benzofuroxan (**Ia**) is shortened from 2.5 h to 30 min, and the yield of benzofurazan (**IIa**) increases from 28 to 58%; likewise, the yield of benzofurazan **IIb** increases from 39 to 48%.

No 5-aminobenzofurazan [5] was detected by TLC in the reduction of 5-nitrobenzofuroxan (**Ib**) with sulfur or its mixture with morpholine, i.e., the reaction is selective. Benzofuroxan **Ib** failed to undergo reduction in acetic acid, while in DMSO only traces of benzofurazan **IIb** were formed.

General procedure for the reduction of benzofuroxans with sulfur. A mixture of benzofuroxan **Ia**–**Ic** or **III** and sulfur in ethylene glycol or a mixture of benzofuroxan **Ia** or **Ib**, sulfur, and morpholine in ethylene glycol was heated at 150–160°C (the amounts of the reactants and reaction time are given in table). The progress of the reaction was monitored by TLC on Silufol UV-254 plates using ethyl acetate–hexane (1:3) as eluent.The mixture was then cooled and diluted with a tenfold volume of water. Benzofurazans **IIa**, **IIb**, and **IV** were isolated by steam distillation, followed by

Reaction conditions and yields of benzofurazans in the reduction of benzofuroxans with sulfur or its mixture with morpholine at 150–160°C

Initial compound no.	Amounts of reactants			Reaction time, h	Product no.	Yield, %	mp, °C (published data)
	benzofuroxan, mol	S, mol	Ethylene glycol, ml				
Ia	0.1	0.1	60	2.5	**IIa**	28	54 (53 [6])
Ia[a]	0.1	0.1	60	1.0	**IIa**	40	54 (53 [6])
Ia[b]	0.1	0.1	60	0.5	**IIa**	58	54 (53 [6])
Ib	0.1	–	100	2.0	**IIb**	5	66 (65.4–66.2 [7])
Ib	0.1	0.5	100	2.5	**IIb**	39	66 (65.4–66.2 [7])
Ib[c]	0.1	0.075	100	2.0	**IIb**	42	66 (65.4–66.2 [7])
Ib[a]	0.1	0.0626	100	2.0	**IIb**	48	66 (65.4–66.2 [7])
Ic[d]	0.02	0.015	30	2.5	**IIc**	50	156 (156 [8])
III[d]	0.02	0.06	60	2.0	**IV**	54	60–61 (61–62 [9])

[a] Morpholine, 0.2 ml.
[b] Morpholine, 0.4 ml.
[c] Morpholine, 0.1 ml.
[d] 145–150°C.

recrystallization from alcohol. Benzofurazan **IIc** separated from the mixture after dilution with water and was filtered off and purified by recrystallization from alcohol.

REFERENCES

1. Levinson, F.S., Evgen'ev, M.I., Ermolaeva, E.A., Efimov, S.I., Falyakhov, I.F., Garipov, T.V., and Karimova, N.G., *Khim.-Farm. Zh.*, 2003, no. 10, p. 12.
2. Ghosh, P.B. and Whitehouse, M.W., *J. Med. Chem.*, 1961, vol. 11, p. 305.
3. Whitehouse, M.W. and Ghosh, P.B., *Biochem. Pharmacol.*, 1968, vol. 7, p. 158.
4. Khmel'nitskii, L.I., Novikov, S.S., and Godovikova, T.I., *Khimiya furoksanov. Reaktsii i primenenie* (The Chemistry of Furoxans. Reactions and Application), Moscow: Nauka, 1983, pp. 50, 51, 57, 58.
5. Dal Monte, D. and Sandri, E., *Boll. Sci. Fac. Chim. Ind. Bologna*, 1964, vol. 22, p. 33.
6. Di Nunno, L.D., Florio, S., and Todesco, P.E., *J. Chem. Soc., Perkin Trans. 1*, 1973, p. 1954.
7. Mollory, F.B. and Varimbi, S.P., *J. Org. Chem.*, 1963, vol. 28, p. 1556.
8. Borsche, W. and Weber, S.P., *Justus Liebigs Ann. Chem.*, 1931, vol. 489, p. 270.
9. Bailey, A.S. and Evans, J.M., *Chem. Ind.*, 1964, vol. 32, p. 1424.