A FACILE SYNTHESIS OF 1-ARYL-2-ARYLTHIO-1*H*-IMIDAZOLES

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Abstract — The reaction between the hitherto unknown 2,2-diethoxy-1-isocyanoethane (**1**) with sulfenyl chlorides (**2**) and arylamines afforded isothioureas (**4**) which were cyclized to give the title compounds.

As it is well known 1-substituted 2-alkylthio- (or arylthio)-1-*H*-imidazoles can be easily prepared by reacting 1,3-dihydro-1-substituted 2*H*-imidazole-2-thiones with alkyl halides or activated aryl halides.[1]

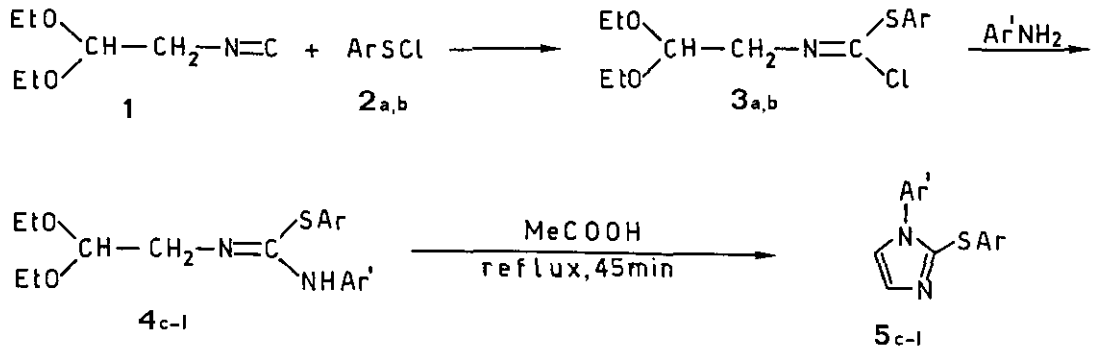
A careful examination of the literature shows that no synthetic method is available for the synthesis of 1-aryl-2-arylthio-1*H*-imidazoles in which the aromatic moiety linked to the sulfur atom does not contain electron-withdrawing groups. In continuation of our studies on the synthesis of heterocyclic compounds starting from isonitriles and compounds containing S-Cl groups,[2] we wish to report a novel synthetic method which allowed us to obtain 1-aryl-2-arylthio-1*H*-imidazoles in high yields with ease.

The present synthesis is based upon the use of 2,2-diethoxy-1-isocyanoethane (**1**), a hitherto unknown isonitrile which was prepared by dehydrating the corresponding *N*-substituted formamide.

The reaction between **1** and arylsulfenyl chlorides (**2**) afforded *N*-(2,2-diethoxyethyl)-*S*-arylisothiocarbamoyl chlorides (**3**) which were reacted in situ with amines to give the corresponding isothioureas (**4**). On heating the crude **4** with acetic acid a ring-closure reaction took place giving 1-aryl-2-arylthio-1*H*- imidazoles (**5**).

Concerning the present synthesis some remarks should be made. Isothiocarbamoyl chlorides (**3**) were obtained in almost quantitative yields even in very mild conditions due to the high reactivity of sulfenyl halides towards the isocyano moiety.[3] The solution of **3** in CH_2Cl_2 was directly employed for the reaction with amines which afforded *S*-arylisothioureas (**4**). Compound **4g** was isolated and characterized,[4] whereas the other isothioureas were obtained as viscous syrups which did not crystallize after standing for several days. It must be noted that the

purification of isothioureas (4) is unnecessary since the cyclization to imidazoles (5) can be performed on the crude product with very good yields.



a Ar = 4-ClC_6H_4
b Ar = 4-$CH_3C_6H_4$
c Ar = 4-ClC_6H_4 Ar' = C_6H_5
d Ar = 4-ClC_6H_4 Ar' = 4-$CH_3C_6H_4$
e Ar = 4-ClC_6H_4 Ar' = 4-$CH_3OC_6H_4$
f Ar = 4-ClC_6H_4 Ar' = 3-ClC_6H_4
g Ar = 4-ClC_6H_4 Ar' = 4-ClC_6H_4
h Ar = 4-ClC_6H_4 Ar' = 3,5-diClC_6H_3
i Ar = 4-$CH_3C_6H_4$ Ar' = C_6H_5
k Ar = 4-$CH_3C_6H_4$ Ar' = 4-$CH_3OC_6H_4$
l Ar = 4-$CH_3C_6H_4$ Ar' = 4-ClC_6H_4

The physical and spectral data of 1-aryl-2-arylthio-1*H*-imidazoles (**5c-l**) prepared are summarized in the Table.

EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. Unless otherwise stated the ^{1}H-nmr spectra were recorded with a Perkin-Elmer R32 apparatus for DMSO-d_6 saturated solutions. Chemical shifts are reported in ppm (δ) from TMS. Ir spectra were measured on a Perkin-Elmer 881 apparatus.

2,2-Diethoxy-1-isocyanoethane (1)

A mixture of aminoacetaldehyde diethyl acetal (50.24 g, 377 mmol) and ethyl formate (33.48 g, 452 mmol) was refluxed for 3 h. The ethanol and the excess ethyl formate were removed under reduced pressure and the residue was distilled in vacuo to give 55.3 g (91 %) of 2,2-diethoxy-1-formylaminoethane,[5] bp 105-107 °C 0.5 mm/Hg; ir (film): 3304, 1666 cm^{-1}. *Anal.* Calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 51.97; H, 9.47; N, 8.72.

A solution of the above material (24.2 g, 150 mmol), CCl_4 (23.07 g, 150 mmol), PPh_3 (44.59 g, 170 mmol) and NEt_3[6] (15.18 g, 150 mmol) in CH_2Cl_2 (150 ml) was refluxed for 3.5 h. The solvent was removed and the residue was stirred with 400 ml of ether. The resulting suspension was allowed to stand overnight at 5 °C and then filtered. The filtrate was evaporated and the residue was distilled to give 17.61 g (81 %) of **1**, colorless, vile smelling oil, bp 45 °C 0.4 mm/Hg; ir (film): 2156 cm^{-1}; ^{1}H-nmr (CCl_4): 4.72-4.58(t, J = 0.6 Hz, 1H, CH), 3.78-3.52(m, 4H, CH_2), 3.44-

TABLE

Physical and spectral data for 1-aryl-2-arylthio-1*H*-imidazoles (5c-l).

	mp °C	Solvent	Yield (%)	Formula	Analysis[a] C	H	N	^{1}H-nmr (DMSO-*d*6)
5c	103-104	EtOH/H_2O	75	$C_{15}H_{11}N_2ClS$	62.83 (62.75)	3.87 (3.76)	9.77 (9.63)	7.73-7.05 (m, H ar. + H im.)[b]
5d	112-114	EtOH/H_2O	77	$C_{16}H_{13}N_2ClS$	63.89 (63.79)	4.36 (4.27)	9.31 (9.24)	7.65-7.02 (m, 10 H, H ar. + H im.), 2.34 (s, 3H, CH_3)
5e	87-89	cyclohexane	80	$C_{16}H_{13}N_2OClS$	60.66 (60.55)	4.14 (4.10)	8.84 (8.79)	7.65-6.98 (m, 10 H, H ar. + H im.), 3.82 (s, 3H, CH_3)
5f	64-65	cyclohexane	65	$C_{15}H_{10}N_2Cl_2S$	56.09 (55.95)	3.14 (3.02)	8.72 (8.63)	7.76-7.03 (m, H ar. + H im.)[b]
5g	110-111	cyclohexane	85	$C_{15}H_{10}N_2Cl_2S$	56.09 (56.15)	3.14 (3.21)	8.72 (8.82)	7.74-7.04 (m, H ar. + H im.)[b]
5h	97-98	cyclohexane	72	$C_{15}H_9N_2Cl_3S$	50.66 (50.69)	2.55 (2.47)	7.88 (7.92)	7.80-7.04 (m, H ar. + H im.)[b]
5i	91-92	cyclohexane	79	$C_{16}H_{14}N_2S$	72.15 (72.03)	5.30 (5.22)	10.52 (10.47)	7.68-6.92 (m, 11H, H ar. + H im.), 2.17 (s, 3H, CH_3)
5k	68-69	petr. ether[c]	82	$C_{17}H_{16}N_2OS$	68.89 (68.79)	5.44 (5.35)	9.45 (9.53)	7.70-6.94 (m, 10H, H ar. + H im.), 3.80 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3)
5l	69-70	petr. ether[c]	80	$C_{16}H_{13}N_2ClS$	63.89 (63.80)	4.36 (4.32)	9.31 (9.27)	7.66-6.92 (m, 10H, H ar. + H im.), 2,18 (s, 3H, CH_3)

[a] The found percentages are reported in parentheses. [b] The integration of the nmr signals was not performed. [c] bp 40-70 °C.

3.37(d, J=0.6 Hz, 2H, NCH_2), 1.27-1.12(m, 6H, CH_3); *Anal.* Calcd for $C_7H_{13}NO_2$: C, 58.72; H,9.15; N, 9.78. Found: C, 58.77; H, 9.00; N, 9.86

1-Aryl-2-arylthio-1*H*-imidazoles (5c-l)

General Procedure: A solution of the appropriate sulfenyl chloride **2** (20 mmol) in CH_2Cl_2 (10 ml) was dropped into a well-stirred solution of **1** (2.86 g, 20 mmol) in CH_2Cl_2 (50 ml) maintaining the temperature at -50 °C. The resulting solution was allowed to stand until the temperature rose to 15 °C and then cooled again at -50 °C. A solution of the appropriate amine (40 mmol) in CH_2Cl_2 (30 ml) was dropped into the above solution maintaining the temperature below -40 °C. The resulting mixture was allowed to react, without removing the cooling bath, until the temperature rose to 20 °C, and then evaporated to dryness. The residue was stirred with 70 ml of ether and 50 ml of water and the phases were separated. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The oily residue was dissolved in 50 ml of acetic acid and then refluxed for 45 min. The solvent was carefully removed under reduced pressure to give the crude **5**.

REFERENCES AND NOTES

1. See for example: K. Hofmann, "The Chemistry of Heterocyclic Compounds", eds. by A. Weissberger, Interscience Publishers Inc., New York, 1953, p. 86, 87, E. F. Elslager, P. Jacob, J. Johnson, and L. M. Werbel, *J. Heterocyclic Chem.*, 1980, **17**, 129.
2. See for example: R. Bossio, S. Marcaccini, and R. Pepino, *Heterocycles*, 1986, **24**, 2003; R. Bossio, S. Marcaccini, and R. Pepino, *Heterocycles*, 1986, **24**, 2411; R. Bossio, S. Marcaccini, and R. Pepino, *Tetrahedron Lett.*, 1986, **27**, 4643. R. Bossio, S. Marcaccini, R. Pepino, C. Polo, and G. Valle, *Synthesis*, 1989, 641.
3. See for example: E. Kuehle, "The Chemistry of the Sulfenic Acids", Georg Thieme Verlag, Stuttgart, 1973, p. 57. R. Schubart, "Houben-Weyl", 4th ed., Vol. XI/1, Georg Thieme Verlag, Stuttgart, 1985, p. 63.
4. Compound **4g**: mp 51-52 °C from EtOH/H_2O. *Anal.* Calcd for $C_{19}H_{22}N_2O_2Cl_2S$: C, 55.21; H, 5.37; N, 6.78. Found: C, 55.45; H, 5.31; N, 6.65.
5. This compound was previously reported by Y. Watanabe, Y. Kamochi, K. Kido, T. Kudo, and A. Nose, *Japan Kokai* 74 36,683 (*Chem. Abstr.*, 1974, **81**, 49584e).
6. Triethylamine was dried over KOH and distilled before using.

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