Notes

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Synthesis of 1-Isocyanomethyl Azoles and Related Compounds

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1-Isocyanomethyl azoles (**14a—f**) were synthesized by the reaction of the corresponding azoles (**11a—f**) with trimethylformamidomethylammonium iodide (**8**), followed by dehydration of the resulting 1-formamidomethyl azoles (**13a—f**) using phosphorus oxychloride or triphenylphosphine/carbon tetrachloride. Furthermore, 1-substituted methyl-5-piperidinomethyltetrazoles (**15a—f**) were prepared by means of the four-component condensation of **14a—f** with formaldehyde, sodium azide, and piperidine.

Keywords——isocyanide; formamide; dehydration; azole; four-component condensation

We became interested in the synthesis of some 1-isocyanomethyl azoles (**14a—f**) during a comparative study of the reactivity of *p*-toluenesulfonylmethyl isocyanide.[1] In connection with the synthesis of isocyanides of this type, **14**, it has been reported that trimethylformamidomethylammonium bromide (**1**)[2] or iodide (**8**)[3] can be used for the preparation of formamidomethyl derivatives (**2**, **4**, **6**, or **9**), which are converted to the corresponding isocyanomethyl compounds (**3**, **5**, **7**, or **10**) by dehydration as shown in Chart 1. This information prompted us to apply **8** to synthesize our desired 1-isocyanomethyl azoles (**14a—f**), using the corresponding azoles (**11a—f**) as starting materials. Thus, imidazoles (**11a** and **b**), triazole (**11c**), benzimidazoles (**11d** and **e**), and benzotriazole (**11f**) reacted smoothly with **8** under reflux in the presence of potassium hydroxide as a base to give the corresponding 1-formamidomethyl azoles (**13a—f**). The yields of the products (**13a—f**) ranged from 45% for

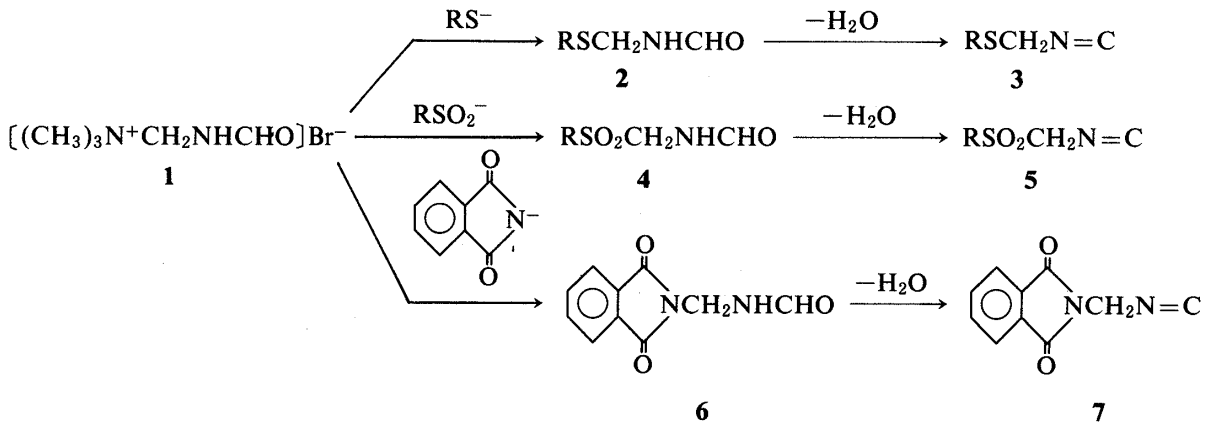


Chart 1

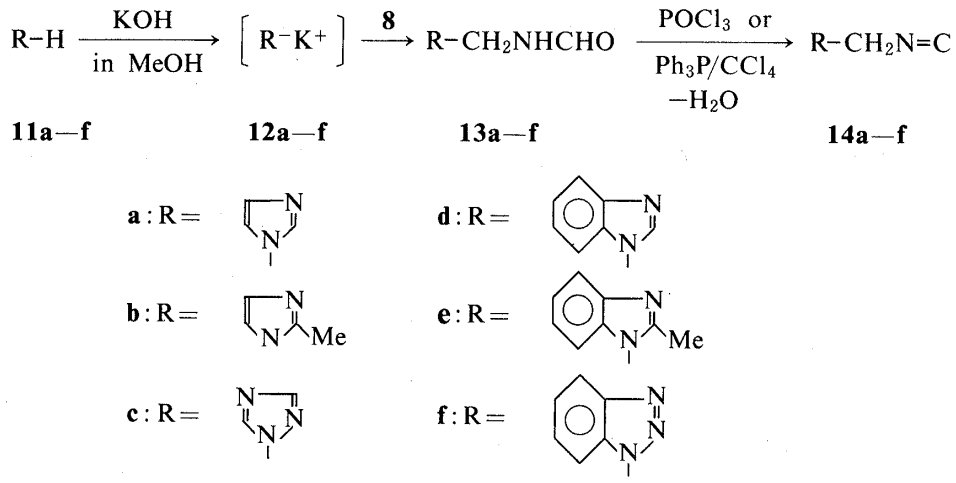


Chart 2

13a and **13b** to 93% for **13f**. Subsequently, dehydration of **13a—f** was achieved by treatment with phosphorus oxychloride($POCl_3$) (method A) or triphenylphosphine/carbon tetrachloride (Ph_3P/CCl_4) (method B)[4] to afford 1-isocyanomethyl azoles (**14a—f**) as shown in Chart 2. A comparison (Table II) of the yields obtained by methods A and B indicates that the yield of each product, **14a—f**, prepared with Ph_3P/CCl_4 was higher than that obtained with $POCl_3$.[5]

Evidence for the structure of each compound, **14a—f**, was provided by the infrared (IR) spectra and mass spectra (MS), which showed a strong characteristic absorption due to the isocyano group at around 2145 cm^{-1} and the appropriate molecular ion peak. To determine accurately the structures of the 1-isocyanomethyl azoles (**14a—f**),[6] **14a—f** were subjected to the reaction with formaldehyde, sodium azide, and piperidine in acidic aqueous acetone for 2 h at room temperature to give the corresponding tetrazoles (**15a—f**) as shown in Table III.

These synthesized 1-isocyanomethyl azoles (**14a—f**), when freshly purified by chromatography on a silica gel column, are colorless and odorless crystalline compounds. However, the 1-isocyanomethyl derivatives (**14a—c**) of imidazole (**11a**), 2-methylimidazole (**11b**), and 1,2,4-triazole (**11c**) are extremely unstable when exposed to air at room temperature, becoming colored with the formation of tarry products. On the other

TABLE I. 1-Formamidomethyl Azoles (**13a—f**) R-CH_2NHCHO

Compd.	Yield (%)	mp (°C)	IR ν_{max}^{KBr} (cm^{-1}) (C=O)	NMR (DMSO-d_6) NH[a]	CHO[b]	-CH_2-	Formula	Analysis (%) Calcd (Found) C	H	N	MS(m/e) M^+
13a	45	62—63	1680	9.00	8.13	5.32[c]	$C_5H_7N_3O$	47.99 (48.11	5.64 5.69	33.58 33.87)	125
13b	45	102—103	1690	9.00	8.11	5.23[c]	$C_6H_9N_3O$	51.78 (51.88	6.52 6.50	30.20 30.39)	139
13c	52	101—102	1670	9.16	8.11	5.51[c]	$C_4H_6N_4O$	38.09 (37.82	4.80 4.67	44.43 44.53)	126
13d	83	153—155	1680	9.10	8.17	5.60[d]	$C_9H_9N_3O$	61.70 (61.91	5.18 5.03	23.99 24.06)	175
13e	72	140—141	1700	8.82	8.10	5.44[d]	$C_{10}H_{11}N_3O$	63.47 (63.74	5.86 5.78	22.21 22.42)	189
13f	93	146—147	1685	9.40	8.20	6.10[d]	$C_8H_8N_4O$	54.54 (54.37	4.58 4.31	31.80 31.89)	176

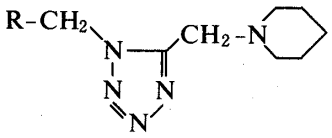
a) Broad singlet. *b*) Doublet, J=1 Hz. *c*) Doublet, J=6 Hz. *d*) Doublet, J=7 Hz.

TABLE II. 1-Isocyanomethyl Azoles (**14a—f**) R-CH_2N=C

Compd.	Yield (%) Method A[a]	Yield (%) Method B[b]	mp (°C)	IR ν_{max}^{KBr} (cm^{-1}) (N=C)	NMR ($CDCl_3$) -CH_2-	Formula	Analysis (%)[c] Calcd (Found) C	H	N	MS (*m/e*) M^+
14a	27	41	42—43	2140	5.49	$C_5H_5N_3$	—	—	—	107
14b	40	67	41—43	2145	5.39	$C_6H_7N_3$	—	—	—	121
14c	31	53	42—44	2150	5.78	$C_4H_4N_4$	—	—	—	108
14d	17	56	133—134	2150	5.63	$C_9H_7N_3$	68.77 (68.96	4.49 4.30	26.74 26.69)	157
14e	36	82	155—157	2140	5.49	$C_{10}H_9N_3$	70.15 (70.11	5.30 5.18	24.55 24.62)	171
14f	71	76	106—107	2140	6.22	$C_8H_6N_4$	60.75 (61.04	3.82 3.73	35.43 35.41)	158

a) Using $POCl_3$. *b*) Using Ph_3P/CCl_4. *c*) See lit. 6.

TABLE III. 1-Substituted Methyl-5-piperidinomethyltetrazoles (**15a—f**)



Compd.	Yield (%)	mp (°C)	NMR ($CDCl_3$) N-CH_2-N	NMR ($CDCl_3$) C-CH_2-N	Formula	Analysis (%) Calcd (Found) C	H	N	MS (*m/e*) $(M+1)^+$
15a	74	106—107	6.71	3.86	$C_{11}H_{17}N_7$	53.42 (53.70	6.93 6.88	39.65 39.78)	248
15b	85	133—134	6.60	3.83	$C_{12}H_{19}N_7$	55.15 (55.41	7.33 7.36	37.52 37.73)	262
15c	78	109—110	7.09	4.06	$C_{10}H_{16}N_8$	48.37 (48.62	6.50 6.51	45.13 45.23)	249
15d	74	173—175	6.90	3.77	$C_{15}H_{19}N_7$	60.58 (60.77	6.44 6.36	32.98 32.90)	298
15e	82	172—174	6.79	3.75	$C_{16}H_{21}N_7$	61.71 (62.01	6.80 6.71	31.49 31.46)	312
15f	76	154—155	7.46	3.94	$C_{14}H_{18}N_8$	56.36 (56.55	6.08 5.96	37.57 37.45)	299

hand, the 1-isocyanomethyl derivatives (**14d—f**) of benzimidazole (**11d**), 2-methylbenzimidazole (**11e**), and 1,2,3-benzotriazole (**11f**) showed the greatest stability on exposure to air, suggesting that the annelation of a benzene ring causes a considerable increase in stability.

Experimental[7]

Preparation of 1-Formamidomethyl Azoles (13a—f)———General Procedure: Trimethylformamidomethylammonium iodide (**8**),[3] (95 g, 0.39 mol) was added portionwise to a stirred solution of one of **11a—f** (0.30 mol) and potassium hydroxide (18.5 g, 0.33 mol) in methanol (300 ml) at room temperature. When the addition was complete, the resulting mixture was refluxed on a water-bath with stirring for 8 h, and then the methanol was evaporated off *in vacuo* to give a heavy syrup. The residue was poured into ethyl acetate (300 ml), and then the insoluble material was filtered off by suction. The filtrate was concentrated to give the appropriate crude product (**13a—f**). **13a** was recrystallized from acetone, and **13b—f** were recrystallized from ethyl acetate to prepare analytical samples. The yields, mp, IR, nuclear magnetic resonance (NMR), MS, and

elemental analysis data for **13a**—**f** are given in Table I. UV λ_{max}^{EtOH} nm (log ϵ): **13d**; 245 (3.83), 273 (3.65), 280 (3.62). **13e**; 245 (4.85), 250 (4.83), 274 (4.68), 281 (4.73). **13f**; 254 (3.80), 260 (3.78), 281 (3.63).

Preparation of 1-Isocyanomethyl Azoles (14a—f)——General Procedure: Method A: The procedure of Böhme[2a] was used with some modifications. A solution of $POCl_3$ (17 g, 0.11 mol) in 1,2-dimethoxyethane (DME) (12 ml) was added dropwise to a suspension of one of the 1-formamidomethyl azoles (**13a**—**f**) (0.10 mol) in a mixture of DME (50 ml), anhydrous ether(20 ml), and triethylamine (70 ml) at 0°C with stirring. After all the $POCl_3$ solution had been added, the resulting mixture was stirred for 30 min at 0°C, and then poured into chilled water (500 ml). The corresponding product (**14a**—**f**) was extracted with three 100 ml portions of dichloromethane (CH_2Cl_2). The extracts were washed with two 50 ml portions of chilled water, and then dried over anhydrous magnesium sulfate. The organic solvents were removed *in vacuo*, affording the crude product (**14a**—**f**) which was developed on a silica gel column with ethyl acetate to give the pure product.

Method B: A suspension of one of **13a**—**f** (0.01 mol), Ph_3P (3.15 g, 0.012 mol), CCl_4 (1.85 g, 0.012 mol), and triethylamine (1.21 g, 0.012 mol) in dry CH_2Cl_2 (10 ml) was gently refluxed for 1 h with stirring. The reaction mixture was cooled, the triethylamine hydrochloride precipitate was filtered off, and then the filtrate was concentrated *in vacuo*. The residue was developed on a silica gel column with ethyl acetate to give the corresponding product, **14a**—**f**. **14d** and **14e** were recrystallized from CH_2Cl_2 to provide analytical samples, and **14f** was recrystallized from benzene. The yields, mp, IR, NMR, and MS for **14a**—**f**, and elemental analysis data for **14d**—**f** are given in Table II. UV λ_{max}^{EtOH} nm (log ϵ): **14d**; 245 (3.87), 274 (3.63), 280 (3.65). **14e**; 243 (4.89), 249 (4.85), 274 (4.65), 281 (4.72). **14f**; 253 (3.82), 266 (3.76), 283 (3.62).

Preparation of 1-Substituted Methyl-5-piperidinomethyltetrazoles (15a—f)——General Procedure: The procedure of Böhme[2a] was used with some modifications. A solution of one of **14a**—**f** (5 mmol) in acetone (10 ml) was added all at once to a stirred suspension of 37% formalin (HCHO, 0.45 g, 15 mmol), piperidine (0.425 g, 5 mmol), and sodium azide (0.325 g, 5 mmol) in a mixture of 3.4 N hydrochloric acid (1.2 ml) and acetone (15 ml) at 5°C. The resulting mixture was stirred for 2 h at room temperature, then acetone (200 ml) was added, followed by supersaturation with potassium carbonate (*ca.* 5 g). The acetone solution was carefully decanted from the insoluble materials and the residue was washed with two 50 ml portions of acetone. The organic solutions were combined, and concentrated *in vacuo*, affording the corresponding crude product (**15a**—**f**), which was recrystallized from CH_2Cl_2 to provide an analytical sample. The yields, mp, IR, NMR, MS, and elemental analysis data for **15a**—**f** are given in Table III. UV λ_{max}^{EtOH} nm (log ϵ): **15d**; 244 (3.34), 274 (3.01), 281 (3.04). **15e**; 244 (3.93), 250 (3.88), 275 (3.64), 281 (3.70). **15f**; 232 (3.94), 256 (3.56), 282 (3.52).

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References and Notes

1) *a*) H. Saikachi, T. Kitagawa, and H. Sasaki, *Chem. Pharm. Bull.*, **27**, 2857 (1979); *b*) H. Saikachi, T. Kitagawa, H. Sasaki, and A.M. van Leusen, *Chem. Pharm. Bull.*, **30**, 4199 (1982).
2) *a*) H. Böhme and G. Fuchs, *Chem. Ber.*, **103**, 2775 (1970); *b*) U. Schöllkopf and R. Schröder, *Tetrahedron Lett.*, **1973**, 633.
3) U. Schöllkopf, R. Schröder, and D. Stafforst, *Justus Liebigs Ann. Chem.*, **1974**, 44.
4) von R. Appel, R. Kleinstück, and Klaus-Dieter Ziehn, *Angew. Chem.*, **83**, 143 (1971).
5) The incomplete extraction of 1-isocyanomethyl azoles (**14a**—**f**) from water into the organic phase may possibly be the reason for the poor yield when $POCl_3$ was used as a dehydrating reagent, because **14a**—**f** are extremely soluble in water, and thus there is strong hydrogen bonding between **14a**—**f** and water.[a] In view of this situation, Ph_3P/CCl_4 has an advantage over $POCl_3$ in that, after solvents are removed from the reaction mixture, the residue can be directly chromatographed for purification without subjecting the reactants to water treatment. *a*) Leading reference; J. Casanova, jun., R.E. Schuster, and N.D. Werner, *J. Chem. Soc.*, **1963**, 4280.
6) Of the 1-isocyanomethyl azoles (**14a**—**f**), **14a**, **14b**, and **14c** were too unstable for elemental analysis to be possible.
7) All melting points are uncorrected. IR spectra were measured on a Hitachi model 260-30 infrared spectrophotometer. NMR spectra were measured on a Nihondenshi model C-100 NMR spectrometer (100 MHz) or a Hitachi R-22 spectrometer (90 MHz) using tetramethylsilane as an internal reference, and chemical shifts were recorded as δ-values. MS were measured on a Hitachi mass spectrometer, model RMU-6MG. UV spectra were measured on a Hitachi 323 spectrometer.