α-Arylazoalkyl Isocyanates and Isothiocyanates by Potassium Permanganate Oxidation of 2,5,5-Trisubstituted 1,2,4-Triazolidin-3-ones and 1,2,4-Triazolidin-3-thiones

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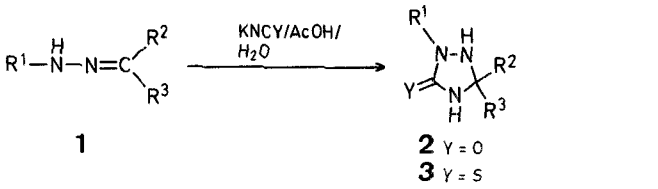
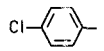
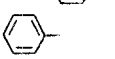
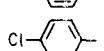
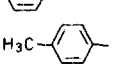
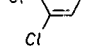
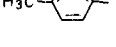
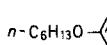
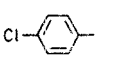
N-Monosubstituted ketone hydrazones **1** react with cyanic acid[1-4] and with thiocyanic acid[4-8] in a [3 + 2]-cycloaddition to give 2,5,5-trisubstituted 1,2,4-triazolidin-3-ones (**2**) and 1,2,4-triazolidin-3-thiones (**3**), respectively. There are scattered reports on the dehydrogenation of compounds **2** which, in the case of the 5,5-disubstituted derivatives ($R^2 = R^3 \neq H$), occurs with concomitant ring opening to provide α-azoalkyl isocyanates. The oxidants employed were chromyl acetate[1], lead(IV) acetate[1], mercury(II) acetate[3], and mercury(II) oxide[2,3]. Some triazolidinones **2** have been reported to be converted into the carbamates[2,3] of the corresponding isocyanates **4** by treatment with an alcoholic solution of bromine or iodine in the presence of sodium alkoxide. Furthermore, the oxidative ring opening of 2-phenyl-5,5-dimethyl-1,2,4-triazolidin-3-thione (**3a**) yields 1-phenylazo-1-methylethyl isothiocyanate (**5a**)[7]. If the 1,2,4-triazolidine-3-thione **3** is only monosubstituted in position 5 ($R^2 = H$), oxidation causes dehydrogenation of the heterocycle and furnishes the corresponding 1,2,4-triazolin-3-thione[6].

Arylhydrazones of aliphatic ketones (**1a–e**) react with a slight excess of potassium cyanate or thiocyanate in dilute acetic acid at room temperature, and are readily transformed into the corresponding 1,2,4-triazolidin-3-ones (**2a–e**), and 1,2,4-triazolidin-3-thiones (**3a–e**). The same applies to alkylhydrazones of aliphatic ketones[9]. Arylhydrazones of alkyl phenyl ketones (**1f–h**) require forced reaction conditions, in particular elevated reaction temperatures, prolonged reaction time, and a considerable excess of potassium cyanate or thiocyanate. Remarkably, attempts to convert acetophenone (2-chlorophenyl)-hydrazone (**1**, $R^1 = 2\text{-Cl-}C_6H_4$, $R^2 = CH_3$, $R^3 = C_6H_5$) into the corresponding heterocycles **2** and **3** failed. Furthermore, benzophenone phenylhydrazone (**1**; $R^1 = R^2 = R^3 = C_6H_5$), as an example of an aromatic ketohydrazone, did not react even under more drastic conditions.



1-5	R^1	R^2	R^3	1-5	R^1	R^2	R^3
a		CH_3	CH_3	e		CH_3	CH_3
b		CH_3	CH_3	f		CH_3	
c		CH_3	CH_3	g		CH_3	
d		CH_3	CH_3	h		CH_3	

The oxidation steps **2** → **4** and **3** → **5** can be accomplished efficiently using potassium permanganate in a two phase system (water/ether). Thus, a 2% aqueous solution of this reagent is mixed with an ether solution or suspension of **2** or **3** to afford the yellow α-arylazoalkyl isocyanates **4** and isothiocyanates **5**, respectively. This procedure appears to be applicable to a wide range of 2,5,5-trisubstituted 1,2,4-triazolidin-3-ones **2** and 1,2,4-triazolidin-3-thiones **3** (R^1 = aryl, alkyl, R^2/R^3 = alkyl/alkyl and alkyl/aryl), and it offers the advantage of simplicity and efficiency, in particular with regard to simple reaction conditions, short reaction time, and high yields (mostly > 90%) of isolated product.

Remarkably, the aqueous reaction medium, even though turning alkaline in the course of the oxidation, does not affect the products **4** and **5**. The reduced reactivity of this type of

Table 1. 2-Aryl-5-methyl-5-phenyl-1,2,4-triazolidin-3-ones **2** and -3-thiones **3** prepared from Acetophenone Arylhydrazones **1**

Product	Yield [%]	m.p. [°C]	Molecular Formula[a]	I.R. ($CHCl_3$) N—H	ν [cm^{-1}][b,c] C=Y	^{1}H-N.M.R. (CDl_3/TMS)[b,d] δ [ppm]
2f	80	178–180°	$C_{15}H_{15}N_3O$ (253.3)	3410–3110	1700(vs)	1.73 (s, 3H, 5-CH_3); 4.70 (s, 1H, NH); 6.36 (br.s, 1H, NH); 7.0–8.0 (m, 10H_{arom})
2g	86	159–160°[e]	$C_{16}H_{17}N_3O$ (267.3)	3400–3200	1700(vs)	1.73 (s, 3H, 5-CH_3); 2.26 (s, 3H, CH_3); 4.70 (s, 1H, NH); 6.43 (br.s, 1H, NH); 6.9–7.7 (m, 9H_{arom})
2h	59	165°	$C_{15}H_{14}ClN_3O$ (287.8)	3430–3220	1705(vs)	1.73 (s, 3H, 5-CH_3); 4.70 (s, 1H, NH); 6.66 (br.s, 1H, NH); 7.0–7.8 (m, 9H_{arom})
3f	74	161–163°	$C_{15}H_{15}N_3S$ (269.4)	3430–3200	1650(br)	1.76 (s, 3H, 5-CH_3); 5.16 (s, 1H, NH); 7.1–8.0 (m, 10H_{arom}); 8.23 (br.s, 1H, NH)
3g	75	178–180°	$C_{16}H_{17}N_3S$ (283.4)	3400–3200	1660(br)	1.76 (s, 3H, 5-CH_3); 2.30 (s, 3H, CH_3); 5.13 (s, 1H, NH); 7.0–7.8 (m, 9H_{arom}); 8.13 (br.s, 1H, NH)
3h	72	181°	$C_{15}H_{14}ClN_3S$ (303.8)	3400–3100	1670(br)	1.76 (s, 3H, 5-CH_3); 5.16 (s, 1H, NH); 7.1–8.0 (m, 9H_{arom}); 8.20 (br.s, 1H, NH)

[a] Satisfactory microanalyses obtained: C ±0.25; H ±0.30; N ±0.38.
[b] Spectral data for products **2a–e** and **3a–e** as reported[4].
[c] Recorded on a Beckman AccuLab 4 spectrometer.
[d] Recorded at 60 MHz using a JEOL PMX-60 spectrometer.
[e] Crystal conversion at 130°C.

Table 3. α-Arylazoalkyl Isocyanates **4** and Isothiocyanates **5** prepared

Product	Reaction time [min]	Yield [%]	b.p. [°C]/torr or m.p. [°C] (solvent)	Molecular Formula[a] or Lit. Data	I.R. (KBr or neat)[b] $\nu_{N=C=X}$ [cm^{-1}]	U.V./Vis (c-C_6H_{12})[c] λ_{max} [nm] (log ε)	^{1}H-N.M.R. ($CDCl_3$ or CCl_4/TMS)[d] δ [ppm]
4a	5	97	54–55°/0.2	128–130°/18[1]; 54–55°/0.2[2]	–	–	–
4b	5	87	81–83°/0.5; 22–25° (pentane)	81–83°/0.5[3]	–	–	–
4c	5	89	45–47° (pentane)	$C_{10}H_9Cl_2N_3O$ (258.1)	2215, 2155	276 (4.08), 389 (2.28)	1.60 (s, 6H, CH_3); 7.4–7.9 (m, 3H_{arom})
4d	5	93	53–55° (pentane)	$C_{16}H_{23}N_3O_2$ (289.4)	2230, 2200, 2150	306 (4.11), 376 (2.49)	0.95 (t, 3H, CH_3); 1.2–2.0 (m, 8H); 1.55 (s, 6H, CH_3); 3.93 (t, 2H, J = 6 Hz); 6.74, 6.89, 7.63, 7.78 (AA'BB', 4H_{arom})
4e	5	94	57–59° (PE 40–60°)	$C_{10}H_{10}N_4O_3$ (234.2)	2220, 2200(sh), 2150	276 (4.26), 388 (2.42)	1.65 (s, 6H, CH_3); 7.80, 7.95, 8.23, 8.38 (AA'BB', 4H_{arom})
4f	10	99	34–36° (pentane)	$C_{15}H_{13}N_3O$ (251.3)	2270(sh), 2210	270 (4.09), 384 (2.27)	1.86 (s, 3H, CH_3); 7.15–8.95 (m, 10H_{arom})
4g	10	92	24–25° (pentane)	$C_{16}H_{15}N_3O$ (265.3)	2270(sh), 2220, 2140	280 (4.11), 400 (2.35)	1.83 (s, 3H, CH_3); 2.33 (s, 3H, CH_3); 7.1–8.8 (m, 9H_{arom})
4h	30	96	oil	$C_{15}H_{12}ClN_3O$ (285.7)	2280(sh), 2330, 2180(sh)	286 (4.16), 385 (2.32)	1.70 (s, 3H, CH_3); 7.0–8.7 (m, 9H_{arom})
5a	5	93	94°/1.2	94°/1.2[7]	–	–	–
5b	5	92	100°/0.04	$C_{10}H_{10}ClN_3S$ (239.7)	2060, 2015, 2000	278 (4.13), 404 (2.28)	1.67 (s, 6H, CH_3); 7.30, 7.43, 7.63, 7.77 (AA'BB', 4H_{arom})
5c	5	94	67–69° (PE 40–60°)	$C_{10}H_9Cl_2N_3S$ (274.2)	2060, 2020, 2000	277 (4.11), 406 (2.30)	1.70 (s, 6H, CH_3); 7.35–7.90 (m, 3H_{arom})
5d	5	94	30–32° (PE 40–60°)	$C_{16}H_{23}N_3OS$ (305.4)	2060, 2000	309 (4.21), 392 (2.53)	0.91 (t, 3H, CH_3); 1.1–2.0 (m, 8H); 1.65 (s, 6H, CH_3); 3.97 (t, 2H, J = 6 Hz); 6.80, 6.95, 7.65, 7.80 (AA'BB', 4H_{arom})
5e	5	97	53–55° (PE 40–60°)	$C_{10}H_{10}N_4O_2S$ (250.3)	2060, 2020, 2000	275 (4.23), 403 (2.40)	1.75 (s, 6H, CH_3); 7.80, 7.95, 8.23, 8.38 (AA'BB', 4H_{arom})
5f	10	99	oil[e]	$C_{15}H_{13}N_3S$ (267.4)	2330(sh), 2010, 2120(sh)	280 (4.11), 400 (2.22)	1.96 (s, 3H, CH_3); 7.2–8.9 (m, 10H_{arom})
5g	10	93	oil[e]	$C_{16}H_{15}N_3S$ (281.4)	2330(sh), 2010, 2120(sh)	285 (4.11), 403 (2.36)	1.96 (s, 3H, CH_3); 2.33 (s, 3H, CH_3); 7.1–8.8 (m, 9H_{arom})
5h	30	97	oil[e]	$C_{15}H_{12}ClN_3S$ (301.8)	2330(sh), 2020, 2130(sh)	287 (4.16), 402 (2.34)	2.00 (s, 3H, CH_3); 7.1–8.8 (m, 9H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.19, N ±0.38; exceptions: **4d**, C +0.52; **4f**, C +0.47.
[b] Recorded on a Beckman AccuLab 4 spectrometer.
[c] Recorded on a Gilford 250 spectrometer.
[d] Recorded at 60 MHz using a JEOL PMX-60 spectrometer.
[e] Decomposes at 130°C.

isocyanates **4** thus compares with that of sterically hindered *t*-alkyl isocyanates[10]. However, prolonged reaction of **2** with an acetone solution of potassium permanganate yields symmetrically disubstituted ureas of the type to be expected from the action of water upon isocyanates; these ureas are also obtained when isocyanates **4** react with hot alkali[4].

The α-arylazoalkyl isocyanates **4** and isothiocyanates **5** show a versatile reactivity since both the heterocumulene function and the azo group can be transformed to give products of synthetic as well as pharmaceutical interest[4, 11].

2-Aryl-5,5-dimethyl-1,2,4-triazolidin-3-ones (2a–e) and 2-Aryl-5,5-dimethyl-1,2,4-triazolidin-3-thiones (3a–e) from Acetone Arylhydrazones (1a–e); General Procedure:

To a solution of the acetone arylhydrazone **1a–e** or its hydrochloride **1**·HCl (20 mmol) in aqueous acetic acid (1/1, 100 ml), an aqueous solution (10 ml) of potassium cyanate (1.78 g, 22 mmol) or potassium thiocyanate (2.13 g, 22 mmol) in water, is added dropwise with stirring. Subsequently, the mixture is diluted with water (100 ml) and stirring is continued (1–2 h). The crystalline product **2a–e**[4] or **3a–e**[4] is filtered off, washed with water (3 × 20 ml) until neutral, and dried.

2-Aryl-5-methyl-5-phenyl-1,2,4-triazolidin-3-ones (2f–h) from Acetophenone Arylhydrazones (1f–h); General Procedure:

To a stirred solution of the acetophenone arylhydrazone **1f–h** (40 mmol) in acetic acid (300 ml) and water (40 ml) at 35 °C, potassium cyanate (16.22 g, 200 mmol) is added in one portion. The progress of the reaction is checked by T.L.C. (silica gel, petrol ether/ether 2/1). Upon completion of the reaction (1–2 h), the solution is carefully diluted with water until a slight cloudiness appears. Cooling with an ice bath induces crystallization of the product, and precipitation is completed by continued slow addition of water (up to 300 ml).

2-Aryl-5-methyl-5-phenyl-1,2,4-triazolidin-3-thiones (3f–h) from Acetophenone Arylhydrazones (1f–h); General Procedure:

This method is a variation of the method described for **2f–h**, with respect to reaction temperature (50 °C), the portionwise addition of potassium thiocyanate (19.44 g, 200 mmol) during 30 min, and the reaction time (4–5 h), which is controlled by T.L.C.

α-Arylazoalkyl Isocyanates (4) and Isothiocyanates (5); General Procedure:

A solution or suspension of 2,5,5-trisubstituted 1,2,4-triazolidin-3-one **2** or 1,2,4-triazolidin-3-thione **3** (2 mmol) in ether (30 ml) and an aqueous solution of potassium permanganate (20 ml, 2%, 2.5 mmol) are mixed by shaking in a separatory funnel or by stirring. After the oxidation is completed (5–30 min) as indicated by T.L.C. (silica gel, petrol ether/ether 9/1), the aqueous layer is separated (the manganese dioxide formed may be dissolved by the addition of sodium hydrogen sulfite) and extracted with ether (2 × 30 ml). The combined ether solutions are washed with water until neutral and dried with magnesium sulfate. The solvent is removed in vacuo, and the residue is the pure (T.L.C., N.M.R.) yellow product **4** or **5**.

A note of caution has to be added: While the 1-arylazo-1-methylethyl isothiocyanates (**5a–e**; $R^2 = R^3 = CH_3$) have been purified by distillation under reduced pressure without decomposition, the 1-arylazo-1-phenylethyl isothiocyanates (**5f–h**; $R^2 = CH_3$, $R^3 = C_6H_5$) unexpectedly decomposed at elevated temperatures and therefore distillation of these compounds is to be avoided.

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