SHORT PAPER

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Solid phase N-alkylation of tetrazoles: a thermal decarboxylation†

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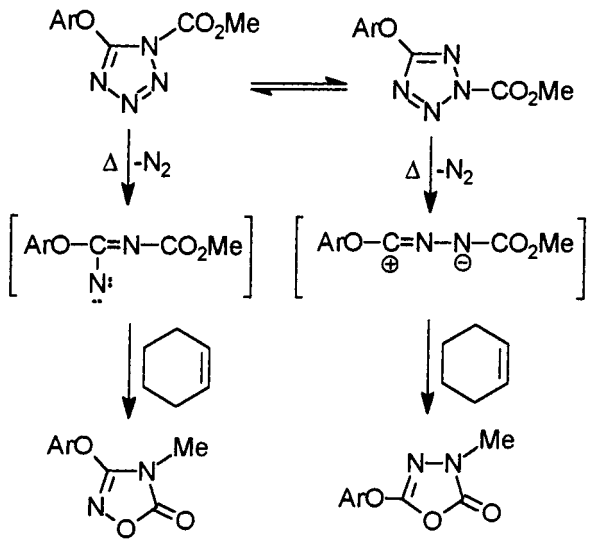
On solid-phase thermal decarboxylation 2-methoxycarbonyl-5-aryloxytetrazoles release carbon dioxide to produce the corresponding 1- and (predominantly) 2-methyl-5-aryloxytetrazoles in high yields and short reaction times.

The chemistry of tetrazoles has gained increasing attention since the early 1980s, mainly due to their role in a variety of synthetic and industrial processes.[1] They are used as pharmacologically active compounds with antihypertensive, antiallergic and antibiotic activities,[2] and as copper corrosion inhibitors.[3] Functionalization of phenyl rings via imidoylnitrenes has been recently reported.[4] Annually, many publications appear on the chemical behavior of tetrazoles and tetrazole derivatives, such as prototopic tautomerism,[5] equilibria of their derivatives,[6] and their photochemical[7] and thermal decomposition.[8–17]

In order to clarify the relationship between structures and thermal properties, Zhou *et al.* recently studied the thermal decomposition and behaviour of mono- and/or di-substituted tetrazoles using the SC–DSC method. They concluded that substitutions at position 1 have less effect on the thermal decomposition temperature and heats of decomposition than those at position 5. They also studied the pressure rise behaviour from thermal decomposition of tetrazoles and their salts and concluded that the thermal decomposition reaction could be accelerated with the increase of the ambient pressure.[18]

Dabbagh and Lwowski recently reported that the thermal decomposition of the equilibrium mixture of *N*-methoxycarbonyl-5-(2,6-dimethylphenoxy) tetrazole in the presence of cyclohexene in refluxing acetonitrile leads to the formation of a 1:1 mixture of oxadiazoles (no nitrene-cyclohexene insertion or decarboxylation was observed) in 61% overall yield, Scheme 1.[6a]



Scheme 1

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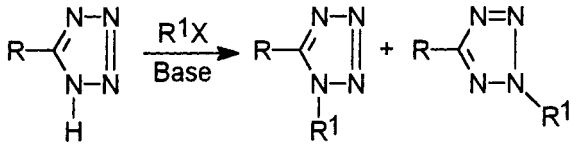
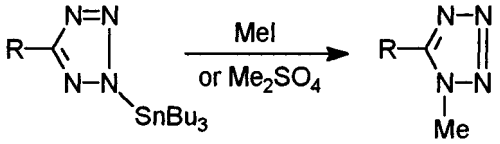
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Methylation of tetrazoles in basic medium leads to the formation of 1- and 2-methyl isomers. In general, it appears that electron-donating substituents at the 5-position tend slightly to favour methylation at position 1 of tetrazole anions, while electron-withdrawing 5-substituents slightly favour position 2 (Scheme 2).[19] In general, it is difficult to predict which site is likely to be the more active for particular tetrazole derivatives.

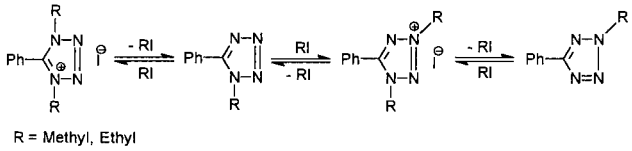


Scheme 2

When methylation is carried out with diazomethane under neutral conditions, the 2-position is sometimes slightly favoured.[20] Selective 1-methylation has been obtained by blocking the 2-position with a tri-*n*-butylstannyl group (Scheme 3). In this case up to 90% methylation at position 1 could be obtained with normal reagents such as methyl iodide and dimethyl sulfate, while the blocking group was removed in the course of the reaction.[21]



Scheme 3



Scheme 4

An interesting conversion of 1-methyl-5-phenyltetrazole into the corresponding 2-methyl isomers by heating with methyl iodide has also been observed. The reaction appears to involve 1,3-dimethyl-5-phenyl tetrazolium salt formation followed by elimination of a molecule of methyl iodide to give the thermodynamically more stable 2-methyltetrazole, Scheme 4.[22]

Table 1 Reaction conditions, melting points, decomposition points of the reactants, products ratio, and solvent system for chromatographic separation of adducts

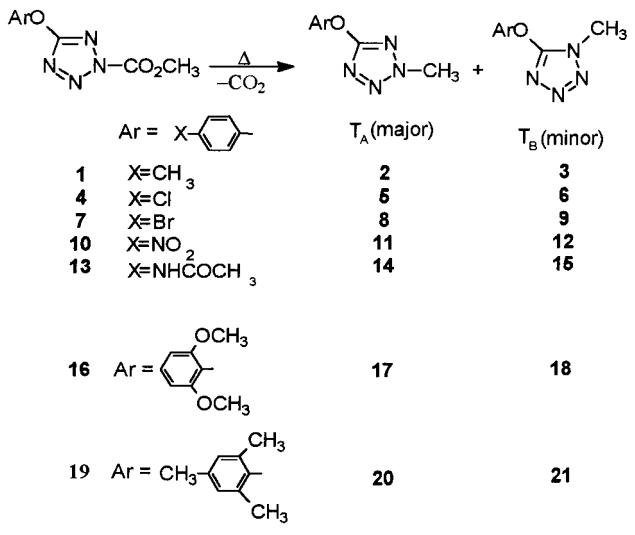
Comp no.	Temperature (°C)	Time (h)	m. p. (°C)[a]	Products Ratio[b] T_A:T_B	Solvent [c]
1	67	10	72–73 (100)	2:1	CCl_4:AcOEt 95:5
4	67	48	90–91 (96–97)	8:5	CCl_4:AcOEt 95:5
7	67	48	77–78 (106)	5:2	CCl_4:AcOEt 90:10
10	85	72	88 (91)	2:1	$CHCl_3$:AcOEt 90:10
13	120	144	109 (110–111)	3:2	$CHCl_3$:AcOEt 70:30
16	70	24	171–173 (125)	2:1	$CHCl_3$:AcOEt 90:10
19	100	48	104–105 (114)	d	C_6H_6:AcOEt 95:5

[a] Decomposition point in parentheses. [b] Calculated from ^{1}H-NMR spectra. [c] Solvent system for chromatography separation of adducts. [d] Was not calculated due to peak overlap.

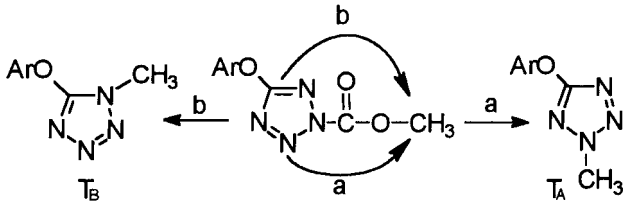
In this work, the thermal decomposition of 2-methyloxycarbonyl-5-aryloxytetrazoles in the solid phase was investigated as a new method for N-methylation of 5-aryloxytetrazoles.

Results and discussion

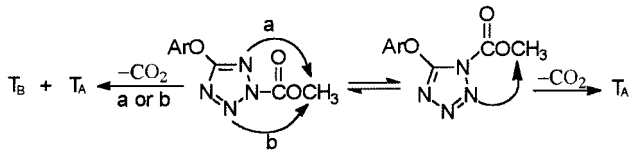
The thermal decarboxylation of 2-methyloxycarbonyl-5-(*p*–X–C_6H_4–O) tetrazoles in solution has been reported as a side reaction.[6b] In the solid phase (during the melting point determination) gas loss was observed below the melting and/or decomposition points without any change in the colour (white) of the tetrazoles. Generally, decomposition of tetrazoles produces a yellow to dark colour. In this work, we decided to examine these observations on a larger scale. It was observed that 2-methoxycarbonyl-5-aryloxytetrazoles, without stirring, gradually released carbon dioxide to give 1- and 2-methyl-5-aryloxytetrazole. The 2-methyl-5-aryloxytetrazoles are the predominant isomers. The reaction conditions, melting points, decomposition points of the reactants, products ratio, solvent composition for chromatography column (for the separation of the products), ^{1}H-NMR, FT-IR, and elemental analysis (CHN) are summarized in Tables 1–3, Scheme 5.



Scheme 5



Scheme 6



Scheme 7

There are two proposed mechanisms: The first is direct loss of carbon dioxide from 2-methoxycarbonyl-5-aryloxytetrazole with migration of the methyl group to the tetrazole 1- (path a) and 2-positions (path b), Scheme 6.

An alternative mechanism is that the 2-methoxycarbonyl-5-aryloxytetrazole equilibrates to a mixture of 1-methoxycarbonyl- and 2-methoxycarbonyl-5-aryloxytetrazole. This mixture then decarboxylates to the methyl tetrazoles (a typical reaction in solution), Scheme 7.[6b]

These reactions can either be concerted, or the methoxycarbonyltetrazole may disassociate to a small extent to the tetrazole anion and CH_3-O-C=O$^+$ cation. The cation can act, not only as an acylating agent, reforming the methoxycarbonyl compound or its isomer, but also as a methylating agent for the anion, releasing CO_2.

Conclusion

Thermal decarboxylation of 2-methoxycarbonyl-5-aryloxytetrazoles in the solid phase releases carbon dioxide and produces 1- and 2- methyl 5-aryloxy tetrazoles at temperatures lower than their normal melting points. The 2-methyl-5-aryloxytetrazoles are the predominant isomers. The high yields, low cost of starting materials, short reaction times, absence of major side products, safety [CH_3I and $(CH_3)_2SO_4$ are carcinogenic], ease of handling and of separation of the products from reaction mixture, are the major advantages of this method.

Table 2 Melting points and results of elemental analysis (CHN) of the thermolysis products

Comp no.	m. p. (°C)	Calcd			Found		
		%C	%H	%N	%C	%H	%N
2	54–55	56.83	5.30	29.46	56.29	5.21	29.27
3	104–105	56.83	5.30	29.46	56.41	5.22	29.35
5	54–56	45.62	3.35	26.60	45.94	3.32	26.79
6	90–91	45.62	3.35	26.60	45.77	3.29	26.49
8	59–60	37.67	2.77	21.96	37.57	2.77	22.37
9	112–114	37.67	2.77	21.96	37.49	2.67	21.93
11	88–90	43.44	3.19	31.66	43.13	3.26	31.67
12	108–109	43.44	3.19	31.66	N.A.	N.A.	N.A.
14	122–124	51.50	4.75	30.03	51.16	4.82	30.27
15	140–142	51.50	4.75	30.03	N.A.	N.A.	N.A.
17	69–70	50.84	5.12	23.72	50.48	5.20	23.61
18	132–133	50.84	5.12	23.72	50.89	5.21	23.15
20	77–78	60.53	6.47	25.67	60.39	6.23	25.82
21	88–89	60.53	6.47	25.67	60.26	6.21	25.64

Table 3 1H-NMR and FT-IR data of decarboxylation reaction products

Comp no.	^{1}H-NMR (ppm)	FT-IR (cm^{-1}) (KBr)
2	δ ($CDCl_3$, CCl_4): 2.35 (s, 3H); 4.20 (s, 3H); 7.20 (s, 4H)	3040(w[a]), 2990(w), 2919(w), 2890(w), 1501(s[b]), 1401(s), 1213(s), 837(w)
3	δ ($CDCl_3$, CCl_4): 2.35 (s, 3H); 3.90 (s, 3H); 7.25 (s, 4H)	3050(w), 2945(w), 2890(w), 1575(s), 1500(s), 1305(s), 1202(m[c]), 870(w)
5	δ ($CDCl_3$, CCl_4): 4.25 (s, 3H); 7.35(AB-quartet, 4H, J=9Hz)	3093(w), 2925(w), 1510(s), 1481(s), 1394(m), 1219(s), 1085(s), 843(s), 783(m), 507(s)
6	δ ($CDCl_3$, CCl_4): 3.90 (s, 3H); 7.40 (s, 4H)	3100(w), 3060(m), 2970(w), 2925(m), 2880(w), 1562(s), 1495(s), 1307(s), 1199(m), 1099(s), 850(s), 790(m)
8	δ ($CDCl_3$, CCl_4):4.30 (s, 3H); 7.45 (AB-quartet, 4H, J=9Hz)	3087(w), 1522(s), 1495(s), 1401(m), 1219(s), 1200(s), 1065(m), 1011(m), 843(s), 776(m), 662(m), 501(m)
9	δ ($CDCl_3$, CCl_4):3.95 (s, 3H); 7.50 (AB-quartet, 4H, J=9Hz)	3085(w), 3060(m), 2940(w), 1549(s), 1488(s), 1307(s), 1193 (m), 1011(m), 850(m), 783(m), 507(m)
11	δ ($CDCl_3$, CCl_4):4.40(s, 3H); 7.55 (d, 2H, J=9Hz); 8.40 (d, 2H, J=9Hz)	3120(m), 3100(m), 1596(m), 1522(s), 1347(s), 1233(s), 1112(m), 857(m), 749(m)
12	δ (DMSO, CCl_4): 4.10(s, 3H); 7.95 (d, 2H, J=9Hz); 8.60 (d, 2H, J=9Hz)	3120(m), 3000(w), 1575(m), 1549(s), 1501(s), 1490(s), 1347 (s), 1300(s), 1253(m), 1112(m), 850(m), 749(m)
14	δ DMSO, CCl_4): 2.15(s, 3H); 4.30 (s, 3H); 7.25 (d, 2H, J=9Hz); 7.75 (d, 2H, J=9Hz); 10.05 (s, 1H);	3308(m), 3220(w), 3170(w), 3080(w), 3030(w), 1683(s), 1528(s), 1500(s), 1401(s), 1199(m), 830(s)
15	δ (DMSO, CCl_4): 2.15 (s, 3H); 4.05 (s, 3H); 7.50 (d, 2H, J=9Hz); 7.85 (d, 2H, J=9Hz); 10.05 (s, 1H);	3310(m), 3281(s), 3214(m), 3150(m), 3073(m), 1690(s), 1562(s), 1508(s), 1414(m), 1306(s), 1266(m), 1206(m), 1018(w), 850(m), 682(w)
17	δ (DMSO, CCl_4): 3.85 (s, 6H); 4.25 (s, 3H); 6.7 (d, 2H, J=9Hz); 7.25 (t, 1H, J=9Hz),	3050(w), 2900(m), 2850(m), 1605(s), 1590(s), 1500(s), 1300(s), 1250(s), 1210(s), 1180(s), 1100(s), 780(s), 740(s), 700(s)
18	δ (DMSO, CCl_4): 3.85 (s, 6H); 4.00 (s, 3H); 6.70 (d, 2H, J=9Hz); 7.25 (t, 1H, J=9Hz)	3050(m), 2990(m), 2980(m), , 2800(m), 1620(s), 1590(s), 1550(s), 1495(s), 1305(s), 1270(s), 1110(s), 780(s), 730(m), 710(m), 650(m)
20	δ ($CDCl_3$, CCl_4): 2.15 (s, 6H); 2.30 (s, 3H); 4.20 (s, 3H); 6.95 (s, 2H)	3030(w), 2970(m), 2925(m), 2890(w), 1522(s), 1401(m), 1199(s), 1139(m), 1031(w), 857(m), 722(m)
21	δ ($CDCl_3$, CCl_4): 2.15 (s, 6H); 2.30 (s, 3H); 3.95 (s, 3H); 7.00 (s, 2H)	3030(w), 2975(w), 2925(m), 2890(w), 1562(s), 1481(s), 1300 (m), 1193(m), 857(w), 649(w)

[a]Band with weak intensity. [b]Band with strong intensity. [c]Band with medium intensity. [d]The FT-IR spectrum was obtained in CCl_4

Experimental section

General: The ^{1}H-NMR spectra were taken on a Varian EM390 (90 MHz).The elemental analysis was performed by Tarbiat Modarres University of Iran. The FT-IR spectra were recorded by Shahreza Azad University of Isfahan. Melting points were taken by the Gallenkamp melting point apparatus. All starting materials and solvents were purified before use. 5-Aryloxy-2-methoxycarbonyl tetrazoles are synthesized according to the method described in references 4 and 6.

Decarboxylation reactions: 5-Aryloxy-2-methoxycarbonyl tetrazoles were placed in a 10 ml round bottom flask and immersed in an oil bath with a fixed temperature without stirring. The reaction progress was monitored by TLC. The resulting mixtures were then subjected to column chromatography and isomeric pairs separated. ^{1}H-NMR and FT-IR data of N-methylated tetrazoles are summarized in Tables 1–3.

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