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A Practical Synthesis of 5-Substituted Tetrazoles.

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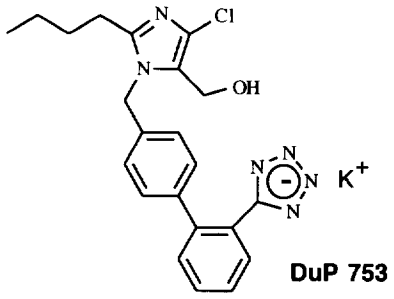
Abstract : Nitrosation of N-formyl amidrazones **8a-g** with sodium nitrite-aqueous hydrochloric acid gives tetrazoles **10a-g** in good yields.

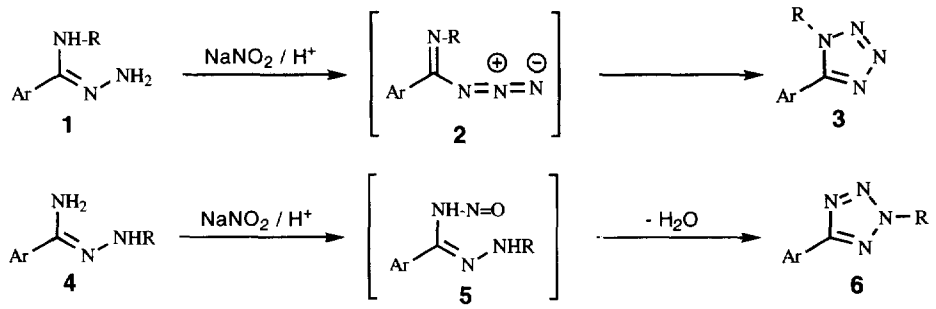
The tetrazole group is similar to the carboxylic function in terms of size and acidity but is apparently more stable metabolically; its use as a carboxylic acid mimic in analogues of biologically active compounds has therefore attracted increasing interest[1] Such derivatives often exhibit different potencies and selectivities in their pharmacological profiles as compared with their carboxylic counterparts. The discovery by researchers at Dupont[2,3] of a promising non peptide angiotensin receptor antagonist containing a 5-aryltetrazole moiety (Dup 753) is only one of many examples arising from the impressive amount of work on these derivatives as can be judged by the number of publications, especially in the patent literature, that have appeared in the past few years.



DuP 753

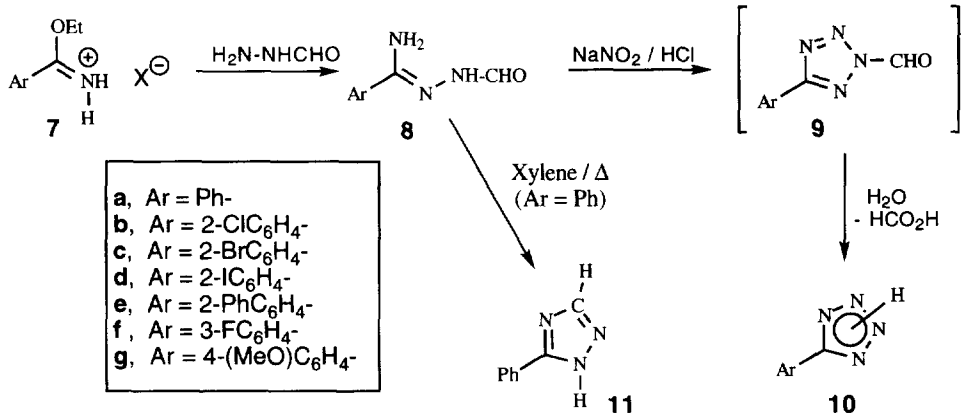
Although most of the effort so far has centered on the preparation of various families of tetrazole derivatives for testing without too much concern for the actual mode of access, finding a practical, scaleable process for building 5-substituted tetrazoles is becoming an important problem. This is a consequence of the fact that, under various guises, essentially all the available methods involve azides[4] with the attending hazards of handling such intermediates or reagents on a large scale. By far the most popular procedure is the classical heating of a nitrile with sodium azide in a variety of solvents in the presence of ammonium salts. Efficient modifications using trialkyl tin (or silicon) azides have also been reported very recently[3,5] Another, less popular but potentially richer approach, consists in nitrosating an amidrazone[6] derivative. This also involves the intermediacy of an azide when the hydrazino nitrogen is

unsubstituted as in **1** (scheme 1). Except for rare cases such as those described by Chattaway and Parkes[7] early in this century, all the examples reported to date belong to this class and are therefore also ill-suited for scale-up. An example of such an approach has been recently reported by the Dupont group where R is a propionitrile group that can be removed as acrylonitrile.[3] In the work of Chattaway and Parkes, the nitrogen substituent R in **4** (scheme 1) is a p-bromophenyl group which is difficult to cleave under mild conditions. In this paper, we wish to report a simple and practical modification of the amidrazone route which does not involve azides and which leads to 5-monosubstituted tetrazoles directly.



Scheme 1

Our approach is based on the fact that a substituent on either of the hydrazino nitrogens would prevent the formation of an azide, but would still allow the cyclisation to the tetrazole as indicated in scheme 2. This auxillary can then be removed in a separate step or, even better, split off under the reaction conditions once the tetrazole ring has been formed.



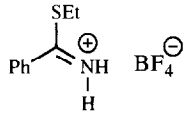
Scheme 2

After some experimentation, we found that the formyl group was quite suitable. The reaction of imidates with N-formyl hydrazine is well known to give 1,2,4-triazoles via the intermediate N-formyl amidrazones which are not isolated.[8] By working at low temperature (0°C) we found the formation of triazole can be avoided and indeed, by operating carefully, we could even isolate the N-formyl amidrazone in the case of **8a** and characterise it completely. As expected, this compound gave the corresponding triazole **11** in 90% yield upon heating in xylene. However, exposure to sodium nitrite in the presence of dilute HCl furnished the desired tetrazole **10a** in almost quantitative yield, presumably via the labile 2-formyltetrazole **9a**. The mechanistic

hypothesis depicted in scheme 2 is only one of several plausible variants and alternatives. Nevertheless, it is unlikely that any of the various possibilities involves the intermediacy of an azide since the hydrazone part is blocked as the N-formyl derivative and, until sodium nitrite is added, this compound is largely unaffected by the mild reaction conditions, as can be shown by the appropriate blank experiments. Moreover, nitrosation would be expected to take place on the more nucleophilic nitrogen as depicted in scheme 2. From a practical viewpoint, the isolation of the intermediate amidrazone is neither necessary nor even desirable; it is most simply and conveniently generated and nitrosated *in situ* . In the case of the phenyl substituted derivative, the overall yield from the imidate salt is very high (95%).

Table. Conversion of imidates **7a-g** into tetrazoles **10 a-g**.

Entry	Imidate	HX (in 7)	Tetrazole	yield (%)	Reference
1	**7a**	HCl	**10a**	95	12
2	**7b**	$HOSO_3Me$	**10b**	65	13
3	**7c**	$HOSO_3Me$	**10c**	60	13
4	**7d**	HBF_4	**10d**	86	13
5	**7e**	HBF_4	**10e**	71	—
6	**7f**	$HOSO_3Me$	**10f**	50	—
7	**7g**	HBF_4	**10g**	75	14
8	**12**	HBF_4	**10a**	52	12

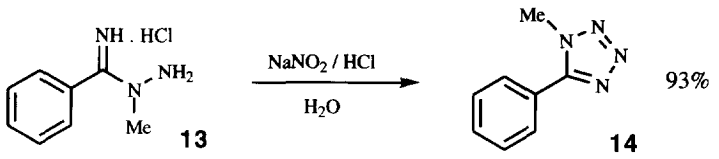


12

This procedure was applied to a number of usefully substituted aromatic imidates prepared in the usual way, either through the Pinner reaction on the corresponding nitrile or by alkylation of the amide with dimethyl sulfate or with Meerwein's triethyloxonium tetrafluoroborate.[9] As can be judged from the results compiled in the Table, yields, although not yet optimised, are generally good. Moreover, the reaction works well with ortho substituted derivatives which tend to be recalcitrant substrates with most of the earlier methods. Of particular importance are o-bromo- and o-iodo-phenyltetrazole (**10c** & **10d**) which can be further elaborated into much more complex structures using the vast possibilities offered by organometallic chemistry. We have also found that a thioimidate such as **12** can also be used to make a tetrazole (entry 8) but the generality of this variant remains to be determined.

In an ancillary study, and as an extension of the work of Chattaway and Parkes,[7] we have found that reacting imidate salt **7a** (hydrochloride) with methyl hydrazine gave interestingly, and at first unexpectedly,[10] compound **13**. Exposure to sodium nitrite/dilute hydrochloric acid in the usual way furnished an excellent yield (93%) of 1-methyl-5-phenyltetrazole **14**. This approach is complementary to the direct methylation of the free tetrazole ring which leads to a mixture of isomers where the 2-methyl isomer dominates.[11]

This approach to tetrazoles allies simplicity and mild experimental conditions; but its greatest asset perhaps is that it does not in principle involve the intermediacy of azides and should therefore be amenable to scale-up with reasonable ease.



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EXPERIMENTAL SECTION

All reactions were performed under an inert atmosphere (nitrogen or argon). Melting points were determined using a Reichert hot stage apparatus. ^{1}H spectra are for deuteriochloroform solutions with tetramethylsilane as internal standard. I.R. spectra are of Nujol mulls unless otherwise stated. Mass spectra (electron impact) were recorded on MS 50 or VG ZAB spectrometers. MATREX 60 (35-70 μm) silica gel was used for column chromatography. Solvents and reagents were purified according to standard laboratory techniques.

N-formyl amidrazone 8a. Formyl hydrazine (0.71g, 11 mmol) was added in several portions over a period of 10 minutes to an ice-cooled suspension of imidate salt **7a** (hydrochloride; 2g, 10 mmol) in pyridine (5 ml). The reaction mixture soon became homogenous. It was allowed to warm up to room temperature over a period of 12 hrs, diluted with water (20 ml), and the solid filtered and recrystallised from water to give the intermediate amidrazone **8a** (1.5g; 85%) ; m.p. 118-119°C (conversion to triazole **11** on heating); ν_{max} 3392, 2925, 1643, and 1598 cm $^{-1}$; ^{1}H nmr (DMSO): δ 3.34 (2H, s), 6.43-6.90 (1H, bs), 7.40 (3H, m), 7.50 (2H, m), 8.35 and 10.21 (total 1H, two rotamers). (Found: C, 57.38; H, 5.25; N, 25.42. Calc. for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75%).

3-Phenyl-1,2,4-triazole 11. Amidrazone **8a** (0.5g) in xylene (5ml) was heated to reflux for 30 minutes. Evaporation of the solvent and purification by chromatography gave triazole **11** (0.45g; 90%) which was recrystallised from ethyl acetate / petroleum ether; m.p. 119°C (lit.[15] m.p. 120 °C).

General procedure for the synthesis of tetrazoles 10a-g.

Formyl hydrazine (11 mmol) was added in several portions over a period of 10 minutes to an ice-cooled suspension of imidate or thioimidate salt (hydrochloride, tetrafluoroborate, methyl sulfate) (10 mmol) in pyridine (5 ml). The reaction mixture soon became homogenous. It was allowed to warm up to room temperature over a period of 12 hrs (in some cases the intermediate precipitates) then cooled in ice, and aqueous hydrochloric acid (1:1, 10ml) was added at such a rate that the temperature of the reaction mixture did not exceed 5°C. The mixture was further cooled (-5°C) and sodium nitrite (0.28 mol) was added portionwise at such a rate that the temperature did not exceed 0°C. Stirring was continued for an additional hour. If the tetrazole precipitated at this point, it was filtered and dried. If no precipitate was apparent, the reaction mixture was extracted with dichloromethane (2 x 30 ml), dried (Na_2SO_4), filtered, and the solvent evaporated. The residue was then purified by column chromatography (petroleum ether:dichloromethane) and the title compound recrystallised from the specified solvent.

5-Phenyltetrazole 10a from benzimidate hydrochloride 7a. The title compound was filtered and dried then recrystallised from ethanol; yield 95 %; m.p. 212-213°C (lit.[12] m.p. 213-215°C).

5-Phenyltetrazole 10a from thiobenzimidate tetrafluoroborate 12. The title compound, identical to an authentic sample, was obtained in 52% yield.

5-(2-Chlorophenyl) tetrazole 10b from 2-chlorophenyl imidate methyl sulfate 7b. The title compound was filtered and dried then recrystallised from methanol/ether; yield 65 %; m.p. 180-181 °C (lit.[13] m.p. 179-180°C).

5-(2-Bromophenyl) tetrazole 10c from 2-bromo-phenyl imidate methyl sulfate 7c. The title compound was filtered and dried. It was recrystallised from methanol / ether; yield 60 %; m.p. 182°C (lit.[13] m.p. 183-184°C); ν_{max} 2922, 1603, 1463 and 1377 cm $^{-1}$. (Found: C, 37.34; H, 2.36; N, 25.2. Calc. for $C_7H_5BrN_4$: C, 37.36; H, 2.24; N, 24.96%).

5-(2-Iodophenyl) tetrazole 10d from 2-iodophenyl imidate tetrafluoroborate 7d. The reaction mixture was extracted with dichloromethane (2 x 30 ml), dried (Na_2SO_4), filtered, and the solvent evaporated. Recrystallisation from methanol yielded the title compound; yield 86 %; m.p. 217°C (lit.[13] m.p. 176-178°C); ν_{max} 2922, 2852, 1600, and 1463 cm $^{-1}$; m/z 272, ($M^{+\cdot}$). (Found: C, 30.91; H,1.85; N, 20.59. Calc. for $C_7H_5IN_4$: C, 31.03; H, 1.96; N, 20.07%).

5-(2-Phenyl)-phenyl tetrazole 10e from (2-phenyl)-phenyl imidate tatrafluoroborate 7e. The reaction mixture was extracted with dichloromethane (2 x 30 ml), dried (Na_2SO_4), filtered, and the solvent evaporated. Purification by column chromatography and recrystallisation from methanol gave the title compound; yield 71 %; m.p. 196-198°C; ν_{max} 2923, 1614, and 1461 cm $^{-1}$; ^{1}H nmr (DMSO): δ 7.20-8.00 (multiplet); m/z 222, ($M^{+\cdot}$). (Found: C, 70.26; H, 4.54; N, 25.21. Calc. for $C_{13}H_{10}N_4$: C, 70.01; H, 4.58; N, 25.46%).

5-(3-Fluorophenyl) tetrazole 10f from 3-fluorophenyl imidate tetrafluoroborate 7f. The reaction mixture was extracted with dichloromethane (2 x 30 ml), dried (Na_2SO_4), filtered, and the solvent evaporated. Purification by column chromatography and recrystallisation from methanol gave the title compound; yield 50 %; m.p. 145°C; ν_{max} 2921, 1591, and 1460 cm $^{-1}$; m/z 164, ($M^{+\cdot}$). (Found: C, 51.06; H, 3.31; N, 33.94. Calc. for $C_7H_5FN_4$: C, 51.22; H, 3.07; N, 34.13%).

5-(4-Methoxy)-phenyl tetrazole 10g from 4-methoxyphenyl imidate tetrafluoroborate 7g. The title compound was filtered. Recrystallisation from methanol gave the title compound; yield 75 %; m.p. 230-231°C (lit.[14] m.p. 232-233°C).

1-Methyl-5-phenyl tetrazole 14. Methylhydrazine (2.2g, 48 mmol) in pyridine (2 ml) was added over a period of 10 minutes to an ice-cooled suspension of imidate **7a** (hydrochloride; 8.9g, 48 mmol), in pyridine (20 ml). Stirring was continued for an additional hour and the precipitated N-benzimidoyl-N-methyl-hydrazine

hydrochloride **13** filtered, washed with ether and dried; yield 6.7g (75%); m.p. 182°C (lit.[10] m.p. 185°C). A portion of this material (2g, 10 mmol) was stirred in ice-cold, dilute HCl (1:1; 20 ml) and sodium nitrite (1g; 14 mmol) was added portionwise at such a rate that the temperature did not rise over 0°C. Stirring was continued at a temperature below 5°C for 30 min. and the resulting mixture extracted with dichloromethane (2 x 20 ml). Drying over sodium sulfate of the organic layer and concentration and purification of the residue by chromatography on silica gave the desired tetrazole **14** (1.6g; 93%); m.p. 102°C (lit.[11] m.p. 103-104°C).

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