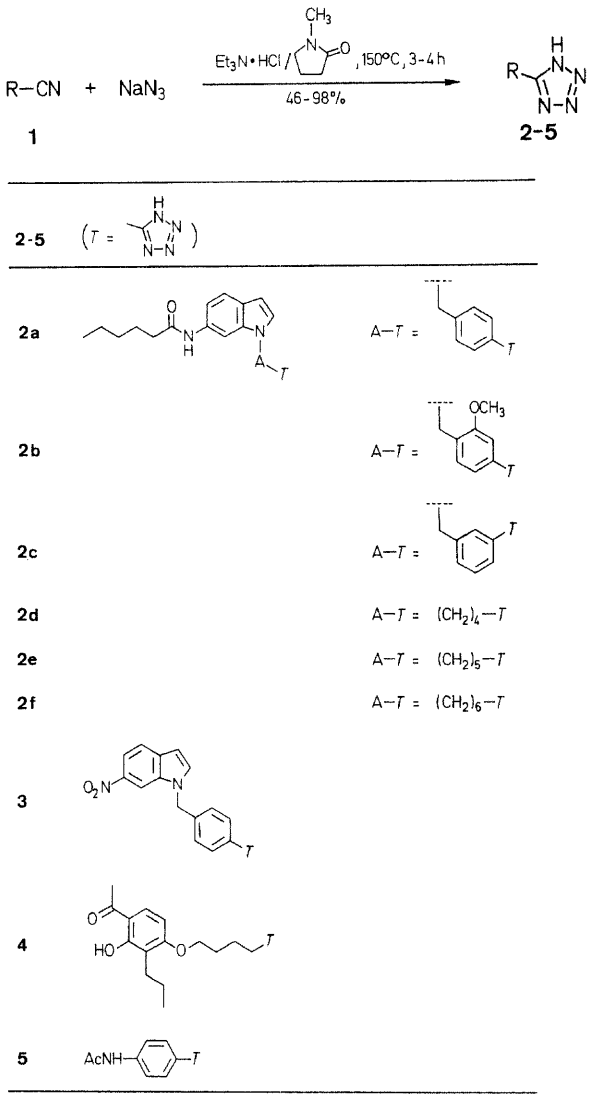

Improved Conditions for the Formation of Tetrazoles

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Tetrazoles can be prepared from nitriles and sodium azide in improved yield over shorter reaction time using triethylammonium chloride as the catalyst and 1-methyl-2-pyrrolidinone as the solvent.

Tetrazoles have long been of interest to the medicinal chemist as possible choices when carboxylic acid mimics were desired.[1] Frequently, these compounds have been similar in activity to the parent acids *in vitro* but have shown different *in vivo* profiles. Recently, LY171883 **(4)**, a leukotriene antagonist which shows enhanced potency and selectivity both *in vitro* and *in vivo* as compared to its parent acid, was described.[2] We decided to prepare the tetrazole analogues of a series of novel acidic leukotriene antagonists, developed in these laboratories, to examine the activity of such compounds.[3]

As a result of those efforts, we now report new reaction conditions which afford enhanced yields of some tetrazoles from nitriles in significantly shorter reaction times. Standard conditions for the formation of tetrazoles from nitriles call for the use of ammonium chloride and sodium azide in dimethylformamide at 125–140°C.[4,5] We have modified these conditions to triethylammonium chloride and sodium azide in 1-methyl-2-pyrrolidinone at 150°C.

When we attempted to convert 1-(4-cyanobenzyl)-6-hexanoylaminoindole to the corresponding tetrazole **2a** using „standard conditions", the result was slow decomposition of the starting nitrile over a period of 24 h. Although aluminum azide in tetrahydrofuran has been reported as a milder reagent for tetrazole formation, it is unsuitable for substrates (such as indoles) which are sensitive to Lewis acids.[6] Because of this, we explored other modifications of the reaction conditions. Variation of the amine hydrochloride catalyst to primary, secondary, or quarternary ammonium halides has been reported for the formation of tetrazoles, with the optimum result occurring with aniline hydrochloride.[4] We tried using aniline hydrochloride in dimethylformamide at 120°C. Monitoring of this reaction by TLC over a 24 h period showed formation of a trace of tetrazole **2a**, no starting nitrile, and much decomposition. A similar result occurred when we used aniline hydrochloride in dimethyl sulfoxide. Use of triethylammonium chloride ($Et_3N \cdot HCl$) in dimethylformamide as the catalyst gave significant product formation, accompanied by both starting material and decomposition. We considered it likely that at least part of the decomposition was cleavage of the amide bond in our substrate by the free nucleophilic amine that exists under the reaction conditions. We also thought that a change in solvent would be

Table 1. Preparation of 5-[4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butyl]tetrazole (**4**, LY 171883) from 5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentanenitrile

Reaction Conditions			Yield[a] (%)	m.p. (°C)[b]
Ammonium Salt/ Solvent	Temp. (°C)	Time (h)		
NH_4Cl/DMF (Lit. [8])	125	23	27	113.5–115
NH_4Cl/DMF (ours)	125	96	35	128–130
$Et_3N \cdot HCl$/NMP	150	3	76	131–132

[a] Yield of isolated product.

[b] Since both we and the original authors[8] had correct analytical data on LY 171883 **(4)** we presume that the difference in melting points is due to crystallization into different polymorphs.

desirable since dimethylformamide is known to produce dimethylamine under similar conditions, e.g. heat and a base (sodium azide).[7] To eliminate these amine sources we tried the use of $Et_3N \cdot HCl$ in 1-methyl-2-pyrrolidinone as solvent. At ~ 150°C, these conditions resulted in clean formation of tetrazole **2a** after only 3 h of reaction time. Tetrazole **2a** was isolated as its hemihydrate in 46% yield following recrystallization.

When we compared the preparation of LY171883 (tetrazole **4**) under the reported[8] standard conditions and under our modified conditions, we found the greatly improved results reported in Table 1.

An additional head-to-head comparison of these modified conditions and the standard protocols was obtained with 4-(6-nitro-1-indolylmethyl)benzonitrile. After a reaction time of 2.5 hours under our new conditions, TLC analysis showed complete conversion of the nitrile and tetrazole **3** was isolated in 55% yield of recrystallized product. As a comparison, after a reaction time of 11 hours under the original conditions significant amounts of the nitrile still remained (yield of tetrazole **3** not determined). In contrast to the above findings, 5-(4-acetylaminophenyl)tetrazole **(5)** was formed from 4-acetylaminobenzonitrile in the same yield (~ 95% before recrystallization) after identical reaction times (3.5 h) using either the standard or our modified conditions.

Table 2. 5-Substituted Tetrazoles **2**–**5** Prepared

Product	Yield[a] (°C)	m.p. (°C)	Molecular Formula[b]
2a	46 (–[d])	134–136	$C_{22}H_{24}N_6O \cdot 0.5H_2O$ (388.5)
2b	43 (67)	210–212	$C_{23}H_{26}N_6O_2$ (418.5)
2c	51 (60)	214–216	$C_{22}H_{24}N_6O$ (388.5)
2d	43 (95)	114–115	$C_{19}H_{26}N_6O$ (354.4)
2e	73 (98)	158–161	$C_{20}H_{28}N_6O \cdot 0.25H_2O$ (368.5)
2f	72 (98)	133–135	$C_{21}H_{30}N_6O$ (382.5)
3	55 (–[d])	230–231	$C_{16}H_{12}N_6O_2 \cdot 0.33H_2O$ (320.3)
4[c]	76 (–[d])	131–132	$C_{16}H_{22}N_4O_3$ (318.4)[c]
5	–[d] (95)	–[d]	$C_9H_9N_5O$ (203.2)

[a] Yield of recrystallized product (yields before recrystallization in parentheses).
[b] Satisfactory microanalyses obtained: C ±0.39, H ±0.11, N ±0.33.
[c] Compound LY 171883; cf. Table 1.
[d] No data.
[e] Lit.[8] m.p. 113.5–115

As shown in Table 2, a variety of other tetrazoles containing an indole moiety were prepared in reasonable yield via the use of these modified conditions.

Melting points are uncorrected. All new compounds were characterized by microanalyses and spectral data: MS, on a Kratos MS-80; IR, on a Perkin-Elmer 727B spectrometer; ^{1}H-NMR, using a Bruker WM-250 spectrometer.

The 1-methyl-2-pyrrolidinone used was Aldrich 99% solvent grade and was dried over 4A molecular sieves before use.

5-[4-(6-Hexanoylaminoindol-1-ylmethyl)phenyl]tetrazole (2a); Typical Procedure:

A mixture of 1-(4-cyanobenzyl)-6-hexanoylaminoindole[3] (350 mg, 1.01 mmol), sodium azide (200 mg, 3.07 mmol), and $Et_3N \cdot HCl$ (212 mg, 1.55 mmol) in 1-methyl-2-pyrrolidinone (10 mL) is stirred at 150°C under N_2 for 4 h. After cooling, the mixture is diluted with H_2O (30 mL), acidified to pH 1 with 10% (w/w) HCl/H_2O [*Caution*: hydrazoic acid], and extracted with EtOAc (2 × 20 mL). The organic layer is extracted with 10% w/w $NaOH/H_2O$ (2 × 10 mL). The alkaline extract is washed with Et_2O (2 × 15 mL), then acidified with HCl, and extracted with EtOAc (2 × 20 mL). This organic extract is evaporated and the solid residue is recrystallized from $MeOH/H_2O$ to afford tetrazole **2a** hemihydrate as a colorless solid; yield: 183 mg (46%); m.p. 134–136°C.

$C_{22}H_{24}N_6O \cdot 0.5\,H_2O$ (388.5, without H_2O)	calc.	C 66.48	H 6.34	N 21.14
(397.5, with H_2O)	found	66.39	6.13	20.94

MS-DCI: *m/e* = 389 (M^+ + 1, 63%), 233 (72), 133 (100).

IR (KBr): ν = 3280 (NH), 1660 (CO) cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS_{int}): δ = 0.86 (t, *J* = 7.5 Hz, 3 H); 1.16–1.37 (m, 4 H); 1.5–1.66 (m, 2 H); 2.25 (t, *J* = 7.5 Hz, 2 H); 5.47 (s, 2 H); 6.47 (d, *J* = 4 Hz, 1 H); 7.17 (d, *J* = 10 Hz, 1 H); 7.36 (d, *J* = 10 Hz, 2 H); 7.62 (m, 2 H); 7.89 (s, 1 H); 8.03 (d, *J* = 10 Hz, 2 H); 9.8 (s, 1 H).

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