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Improved conditions for converting sterically hindered amides to 1,5-disubstituted tetrazoles

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ABSTRACT

Improved conditions for converting amides into 1,5-disubstituted tetrazoles are described. The optimum reaction conditions [diisopropyl azodicarboxylate (DIAD), diphenylphosphoryl azide (DPPA), and diphenyl-2-pyridyl phosphine in THF at 45 °C] converted sterically hindered amides to their corresponding tetrazoles in good yield.

Tetrazoles, while not found in nature, have gained considerable popularity in drug discovery efforts.[1] 5-Substituted (1*H*)-tetrazoles possess an acidic hydrogen at the *N*-1 position and have thus found use as carboxylic acid bioisosteres. While maintaining similar pK_a values to carboxylic acids, 5-substituted (1*H*)-tetrazoles can benefit from improved cell permeability, bioavailability, and metabolic stability. Substitution of the *N*-1 nitrogen to give 1,5-disubstituted tetrazoles has also proven beneficial in drug discovery as *cis*-amide isosteres.[2]

In the context of our medicinal chemistry efforts, we sought to convert sterically hindered amides into their corresponding 1,5-disubstituted tetrazoles using the conditions described in the literature [triphenylphosphine, diethyl azodicaboxylate (DEAD), TMS-azide].[3] Unfortunately, these conditions gave only trace amounts of the desired tetrazoles. Conversion of the primary amide into the (1*H*)-tetrazole followed by alkylation was deemed undesirable as regiochemical mixtures of N-alkylated products are frequently obtained. In this Letter we describe improved reaction conditions for the generation of 1,5-disubstituted tetrazoles from amides.[4,5]

Isopropyl amide **1a** was chosen as a model system to investigate improved tetrazole-forming reaction conditions. We recognized the similarity between the previously reported conditions for converting an amide to a tetrazole[3] to the conditions typically used in a Mitsunobu reaction. We therefore turned to the Mitsunobu literature to guide our efforts and began by exploring a variety of phosphines in the place of triphenylphosphine (Table 1). Polymer-bound triphenylphosphine failed to give the desired product even when less sterically hindered amides were employed (entry 2). It has been reported that electron-rich alkyl phosphine ylides are more reactive than those generated with triphenylphosphine.[6] Unfortunately, phosphines such as diphenylmethyl phosphine gave, not surprisingly, the reduction of TMS-azide (entry 3). Electron-deficient phosphines simply gave no or trace reaction (entries 4–6). Diphenyl-2-pyridyl phosphine has been reported as a viable triphenylphosphine surrogate in the Mitsunobu reaction.[7,8] While reaction at room temperature gave very low conversion (5%) after stirring for 2 h, the use of diphenyl-2-pyridyl phosphine at slightly elevated temperatures gave enhanced conversion (40%) to the desired tetrazole **2a** (entries 7 and 8). The use of diphenyl-2-pyridyl phosphine was also advantageous with respect to reaction work-up and purification. We frequently found it difficult to remove the triphenylphosphine oxide by-product from the desired compounds by column chromatography. As polymer-bound triphenylphosphine failed in our hands, we turned to diphenyl-2-pyridyl phosphine to provide complimentary affinity for silica gel which facilitated our purifications. Such a benefit has been reported previously.[9]

Next, we examined trimethylsilylazide alternatives and found diphenylphosphoryl azide (DPPA) to be a suitable replacement in forming tetrazole **2a**.[10] In the presence of diphenyl-2-pyridyl phosphine and DPPA, 25% conversion of amide **1a** to tetrazole **2a** could be achieved after stirring at room temperature for 2 h (entry 9). The previously described temperature effect could then be exploited to give nearly 50% conversion after 2 h at 45 °C (entry 10). In contrast to reactions with trimethylsilyl azide, reactions with DPPA were homogeneous. We believe that the generation of a homogeneous reaction solution contributes to the increased conversion achieved with DPPA.

Alternative solvents such as 1,2-dimethoxyethane and 1,4-dioxane failed to give improved results (data not shown). Finally, we explored increasing the number of equivalents of all three reagents (diphenyl-2-pyridyl phosphine, DIAD, and DPPA) relative to the substrate. A steady increase in the conversion was observed as the equivalent was increased from two to five (entries 11–13). At 45 °C, it was found that 4 equiv of the reagents was sufficient to drive the reaction to complete conversion after stirring overnight. Under these conditions, tetrazole **2a** could be isolated in 85% yield following column chromatography. To conclude, the use of DPPA, diphenyl-2-pyridyl phosphine, and DIAD (4 equiv each) in THF at

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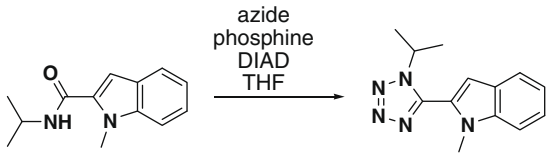
Table 1
Optimization of the conversion of amide **1a** to give 1,5-disubstituted tetrazole **2a**[a]



1a **2a**

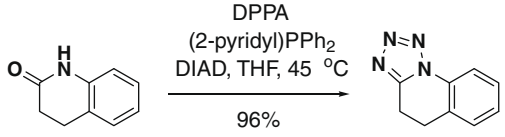
Entry	Phosphine	Azide	Temp (°C)	Equivalents	% Conversion[b] (2 h)
1	Triphenylphosphine	TMS-N_3	25	2	<5
2	Polymer-triphenylphosphine	TMS-N_3	25	2	0
3	Diphenylmethyl phosphine	TMS-N_3	25	2	0
4	Trifurylphosphine	TMS-N_3	25	2	0
5	Triphenylphosphite	TMS-N_3	25	2	<5
6	Tri(4-fluorophenyl)phosphine	TMS-N_3	25	2	<5
7	Diphenyl-2-pyridyl phosphine	TMS-N_3	25	2	5
8	Diphenyl-2-pyridyl phosphine	TMS-N_3	45	2	40
9	Diphenyl-2-pyridyl phosphine	DPPA	25	2	25
10	Diphenyl-2-pyridyl phosphine	DPPA	45	2	49
11	Diphenyl-2-pyridyl phosphine	DPPA	45	3	61
12	Diphenyl-2-pyridyl phosphine	DPPA	45	4	67 (100)[c]
13	Diphenyl-2-pyridyl phosphine	DPPA	45	5	88

[a] All reactions were performed in THF (0.2 M) under nitrogen with equimolar amounts of the indicated phosphine, DIAD, and azide.
[b] % Conversions were determined by LC–MS.
[c] % Conversion after 24 h.

45 °C overnight was adopted as the optimum reaction conditions for converting sterically hindered amide **1a** to 1,5-disubstituted tetrazole **2a**.

With improved conditions in hand, we explored the scope of the reaction. First, we examined different amide substituents as shown in Table 2. Methyl- and ethyl-substituted amides (**1b, 1c**) performed extremely well and gave the corresponding tetrazole products in 70% and 84% yield, respectively (entries 2 and 3). The cyclopropyl amide **1d** could be converted to tetrazole **2d** in 56% yield (entry 4). The limits of this transformation were met with *tert*-butyl amide **1e**. In this case, none of the desired product was observed by LC–MS (entry 5).

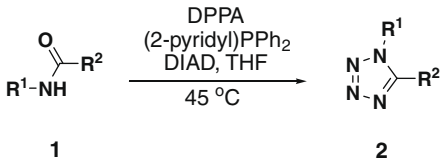
Next, we explored the steric demands of the carboxy substituent. 4-Methyl phenyl analog **1f** could be converted to tetrazole **2f** in good yield (67%, entry 6). Moving the methyl substituent from the *para* to the *ortho* position was well tolerated and amide **1g** gave the corresponding tetrazole in excellent yield (84%, entry 7). Increasing the steric demands by the addition of a second *ortho* methyl substituent as in 2,6-dimethylphenyl compound **1h** also gave good results. In this case, we were pleased to find that the desired tetrazole **2h** could be isolated in 74% yield (entry 8). Aliphatic amides were tolerated as demonstrated by benzyl amide **1i** to give tetrazole **2i** in 73% isolated yield (entry 9). The steric limits of the reaction were met when a quaternary center was placed next to the carbonyl as in example **1j**. In this case, the highly congested tetrazole **2j** was obtained in 30% yield (entry 10). Finally, lactam **1k** was found to be a suitable substrate for this reaction giving tricycle **2k** in high yield.



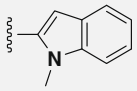
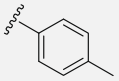
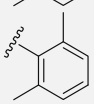
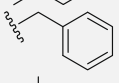
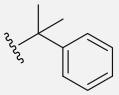
1k **2k**

In conclusion, we have described improved reaction conditions for converting sterically hindered amides to their corresponding 1,5-disubstituted tetrazoles. We believe the mechanism of this reaction follows that which has been described previously.[3] We have successfully applied these conditions in our medicinal chemistry efforts to generate biologically active 1,5-disubstituted tetrazoles as *cis*-amide bond surrogates. These results will be published in due course.

Table 2
Preparation of tetrazoles **2a–j**



1 **2**

Entry	Amide, R^1	R^2	Product, isolated yield (%)
1	**1a** –$CH(CH_3)_2$		**2a**, 85
2	**1b** –CH_3		**2b**, 70
3	**1c** –CH_2CH_3		**2c**, 84
4	**1d** Cyclopropyl		**2d**, 56
5	**1e** –$C(CH_3)_3$		**2e**, 0
6	**1f** –CH_3		**2f**, 67
7	**1g** –CH_3		**2g**, 84
8	**1h** –CH_3		**2h**, 74
9	**1i** –CH_3		**2i**, 73
10	**1j** –CH_3		**2j**, 30

See Ref. 11 for a typical reaction procedure.

References and notes

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4. Sterically hindered 1,5-disubstituted tetrazoles have been prepared by metal triflate catalyzed reaction of alkenes, NBS, nitriles, and $TMSN_3$ to give bromo substituted tetrazoles. The bromide could then be removed by reduction with tributyltin hydride. See: Hajra, S.; Sinha, D.; Bhowmick, M. *J. Org. Chem.* **2007**, *72*, 1852–1855.
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11. *Typical reaction procedure:* A test tube was charged with the amide (1 equiv) and diphenyl-2-pyridyl phosphine (4 equiv). The tube was flushed with nitrogen, and THF (0.2 M) was added followed by the dropwise addition of diisopropyl azodicarboxylate (4 equiv). Diphenylphosphoryl azide (4 equiv) was then slowly added dropwise to the homogeneous solution. *CAUTION:* exotherm. The solution was left to stir in a 45 °C oil bath for 24 h. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (Isco column) eluting with diethyl ether/hexane mixtures to give the desired compounds.