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A Modified Approach to 2-(*N*-Aryl)-1,3-oxazoles: Application to the Synthesis of the IMPDH Inhibitor BMS-337197 and Analogues

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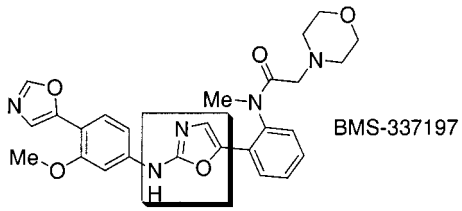
ABSTRACT



A modified approach to the synthesis of 2-(*N*-aryl)-1,3-oxazoles, employing an optimized iminophosphorane/heterocumulene-mediated methodology, and its application to the synthesis of BMS-337197, a potent inhibitor of IMPDH, are described.

The 2-amino-1,3-oxazole moiety is associated with a broad spectrum of biological activity, e.g., antifungal, antibacterial, and antiviral.[1] We recently reported on the identification of BMS-337197 as a potent inhibitor of inosine monophosphate dehydrogenase (IMPDH).[2] The central 2-amino-1,3-oxazole moiety is the key structural element in BMS-337197. However, there are only a few methods known for the synthesis of 2-(*N*-aryl)-substituted 1,3-oxazoles.[3a−d]

For example, Froyen[3b] and Molina[3c] have reported the synthesis of 2-(*N*-phenyl)-substituted 1,3-oxazoles via a tandem iminophosphorane/heterocumulene-mediated annulation.

Ibata and co-workers[3d] have employed a $Rh_2(OAc)_4$-catalyzed reaction of α-diazoacetophenones with *N*,*N*-disubstituted cyanamides to give the corresponding 2-(*N*,*N*-disubstituted)-5-aryloxazoles. However, the reaction gave low yields with monosubstituted cyanamides. For the purpose of synthesizing BMS-337197 and analogues, the iminophosphorane/heterocumulene-mediated synthesis of 2-(*N*-phenyl)-1,3-oxazoles[3b,c] appeared particularly appealing since the reaction is carried out under mild conditions and leads to high yields of the product (Scheme 1). This is particularly true when R_1 in the β-ketoazide (I, Scheme 1) is a phenyl group that is unsubstituted or has an electron-donating substituent like methoxy or methyl. However, very few 2-(*N*-aryl)-substituted 1,3-oxazoles have been made employing this method and therefore the scope and limitations of the reaction have not been completely studied. For example, we found that nitrophenyl-substituted β-ketoazides (I, Scheme 1, R_1 = *o*-nitrophenyl) do not undergo the cyclization reaction under the reported conditions (CH_2Cl_2/room temperature, vide infra).

Retrosynthetically, compounds (**1**) and (**2**) would be the ideal precursors to achieve the synthesis of BMS-337197

(1) Peshakova, L. S.; Kalcheva, V. B.; Simov, D. A. *Chem. Heterocycl. Compd.* **1982**, 741−752.

(2) Dhar, T. G. M.; Shen, Z.; Guo, J.; Liu, C.; Watterson, S. H.; Gu, H. H.; Pitts, W. J.; Fleener, C. A.; Rouleau, K.; Sherbina, N. Z.; Mcintyre, K. W.; Witmer, M.; Tredup, J. A.; Chen, B. C.; Zhao, R.; Bednarz, M. S.; Cheney, D.L.; MacMaster, J. F.; Miller, L. F.; Berry, K. K.; Harper, T. W.; Barrish, J. C.; Hollenbaugh, D. L.; Iwanowicz, E. J. *J. Med. Chem.* **2002**, *45*, 2127−2130.

(3) (a) Van Leusen, A. M.; Jeuring, H. J.; Wildeman, J.; Nispen van, P. J. M.S. *J. Org. Chem.* **1981**, 2069−2072. (b) Froyen, P. *Phosphorous, Sulfur Silcon Relat. Elem.* **1991**, *60*, 81−84. (c) Molina, P.; Fresneda, P. M.; Almendros, P. *Synthesis* **1993**, 54−56. (d) Fukushima, K.; Ibata, T. *Heterocycles* **1995**, 149−154.

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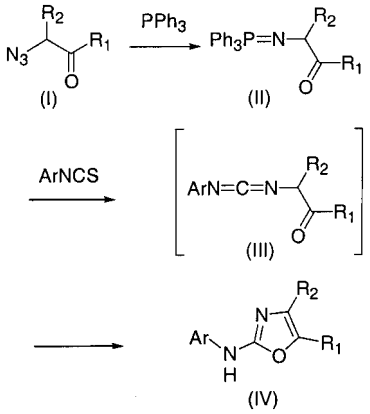
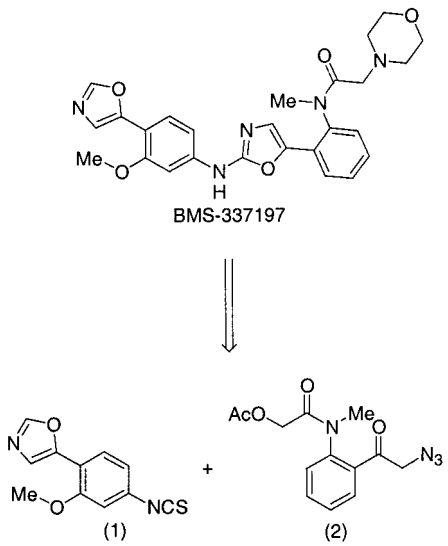
Scheme 1



via the iminophosphorane/heterocumulene-mediated annulation (Scheme 2). The isothiocyanate (**1**) was synthesized

Scheme 2



employing a known literature procedure.[4] The β-keto azide (**2**) was synthesized employing the protocol outlined in Scheme 3. Treatment of *o*-bromoaniline with acetoxyacetyl chloride followed by methylation gave the *N*-methyl amide (**3**) in quantitative yield. Stille coupling of (**3**) with tributyl-(1-ethoxyvinyl)tin gave the enolether (**4**). Reaction of the enolether with *N*-bromosuccinamide in water gave the β-keto bromide, which when treated with sodium azide afforded the key intermediate (**2**), which was set for the iminophosphorane/heterocumulene-mediated annulation.

Reaction of the β-keto azide (**2**) with the isothiocyanate (**1**) under the reported conditions[3b] (CH_2Cl_2/rt) gave the desired 2-(*N*-aryl)-1,3-oxazole (**5**) in 20% isolated yield accompanied by a number of byproducts, which were not characterized. Use of the more reactive and less bulky tributylphosphine[3c] did not improve the yield or the spectrum of byproducts obtained. Hypothesizing that the low yield in the cyclization step might be due to incomplete iminophosphorane formation (I to II, Scheme 1), we decided to run the reaction at a higher temperature.

We were gratified to find that heating a mixture of the isothiocyanate (**1**), β-keto azide (**2**), and triphenylphosphine in dioxane to 90 °C resulted in the formation of the desired 2-(*N*-aryl)-1,3-oxazole (**5**) in 95% isolated yield.[5−7] It is possible that heating the reaction mixture also aids in the cyclization of the carbonyl group (or the enol form) across the carbodiimide (III to IV, Scheme 1). After achieving this key transformation in high yield, the synthesis of BMS-337197 was completed in a two-step sequence as outlined in Scheme 3. We employed this sequence for the synthesis of gram quantities of BMS-337197 to support its further development.

To further explore the structure activity relationships in this series, we had to incorporate electron-withdrawing groups (e.g., nitro and ester) on the 5-phenyl moiety of BMS-337197 (Table 1, entries 1 and 2). However, when the *o*-nitro-β-keto azide (**6**) and isothiocyanate (**1**) were subjected to the iminophosphorane/heterocumulene-mediated annulation in the presence of triphenylphosphine under the reported conditions,[3b] there was no trace of the desired 2-(*N*-phenyl)-1,3-oxazole (**10**). One plausible explanation could be that the electron-withdrawing nitro group on the aromatic ring decreases the electron density across the carbonyl group of intermediate III (Scheme 1) thus preventing the cyclization to the desired product. However, when the reaction was carried out using the optimized conditions (dioxane, 90 °C), it proceeded in the desired fashion to yield 2-(*N*-aryl)-1,3-oxazole (**10**) in 70% isolated yield. In a similar manner, reaction of the β-keto azide **7**, bearing an electron-withdrawing ester group at the ortho position, gave the desired 2-(*N*-aryl)-1,3-oxazole (**11**) in 50% isolated yield. As Table 1 reveals, these optimized reaction conditions can also be applied to the synthesis of 2-(*N*-aryl)-1,3-oxazoles bearing a nonaromatic heterocycle at the C-5 position of the oxazole (Table 1, entry 3) and to isothiocyanates having electron-withdrawing substituents (Table 1, entries 4−6). Although

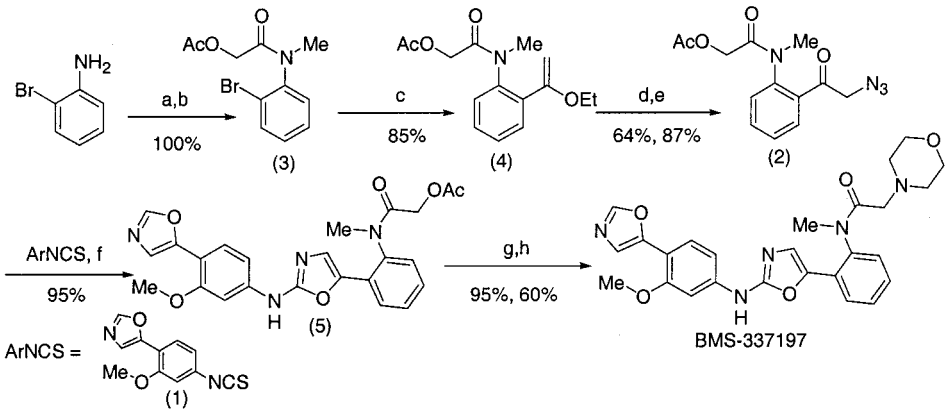
(4) Armistead, D. M.; Badia, M. C.; Bemis, G. W.; Bethiel, R. S.; Frank, C. A.; Novak, P. M.; Ronkin, S. M.; Saunders: J. O. Patent WO9740028, 1997.

(5) **General experimental procedure** for the modified iminophosphorane/hetrocumulene-mediated cyclization (e.g., prepartion of compound (**3**), Scheme 3): To a solution of (**2**) (1.7 g, 5.68 mmol) and 3-methoxy-4-(5-oxazolyl)phenyl isothiocyanate (**1**) (1.1 g, 4.74 mmol) in anhydrous dioxane (10 mL) was added triphenylphosphine (1.5 g, 5.68 mmol). The contents were immersed into a preheated oil bath maintained between 90 and 100 °C and heated at that temperature for 15 min. The reaction mixture was concentrated under reduced pressure and partitioned between 6 N HCl (30 mL) and ethyl acetate (30 mL). The aqueous layer was cooled to 0 °C, made basic using 20% KOH, and extracted into ethyl acetate (2 × 50 mL). The ethyl acetate layer was dried over sodium sulfate and purified using silica gel column chromatography (hexane/ethyl acetate) to yield the title compound (2.1 g, 95%). ^{1}H NMR (DMSO-d_6): δ 10.7 (s, 1H), 8.35 (s, 1H), 7.00−7.8 (m, 9H), 4.4 (d, J = 15 Hz, 1H), 4.1 (d, J = 15 Hz, 1H), 3.9 (s, 3H), 3.1 (s, 3H), 2.0 (s, 3H). HRMS (ESI) calcd for $C_{26}H_{27}N_5O_5$ $(M + H)^+$ 490.2091, found 490.2087.

(6) Although we did not experience any explosions while doing this reaction at 90 °C in dioxane, extreme care should be exercised while heating an azide solution because of the possibility of explosions.

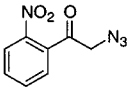
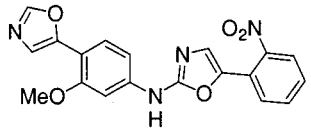
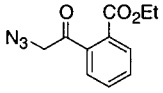
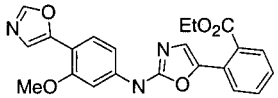
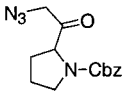
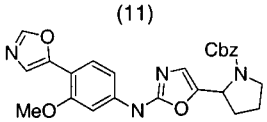
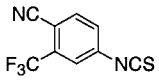
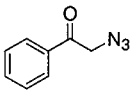
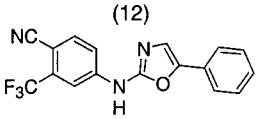
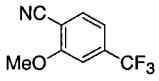
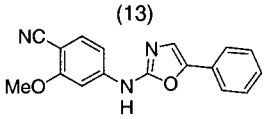
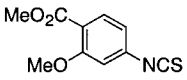
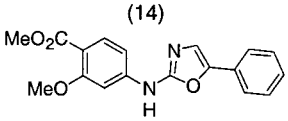
(7) All compounds were of ≥98% purity by LC/MS and analytical HPLC systems.

Scheme 3[a]



[a] (a) $ClCOCH_2OAc$, pyridine, CH_2Cl_2, 2 h; (b) NaH, MeI, DMF, 1 h; (c) $Pd(PPh_3)_2Cl_2$, $CH_2C(OEt)(Bu_3Sn)$, dioxane, 100 °C, 18 h; (d) NBS, H_2O, 50 °C, 10 min; (e) NaN_3, acetone, H_2O, rt, 30 min.; (f) PPh_3, dioxane, 90 °C, 15 min.; (g) LiOH, MeOH, H_2O, rt, 30 min; (h) MsCl, Et_3N, THF, 1 h, then morpholine, Et_3N, DMF, rt.

Table 1. Modified Approach to the Synthesis of 2-(*N*-Aryl)-1,3-oxazoles

entry	isothiocyanate	β-ketoazide	product	yield %
1	1	 (6)	 (10)	70
2	1	 (7)	 (11)	50
3	1	 (8)	 (12)	53
4		 (9)	 (13)	50
5		(9)	 (14)	67
6		(9)	 (15)	69

the yields are moderate, this optimized procedure represents a significant advance in the synthesis of 2-(*N*-aryl)-1,3-oxazoles that are not accessible by earlier reported methods.

In conclusion, a high yielding synthesis of BMS-337197 has been achieved that employs an optimized iminophosphorane/heterocumulene-mediated methodology. This method has been used to prepare a variety of 2-(*N*-phenyl)-1,3-oxazoles for the IMPDH program. Notably, this reaction can now be carried out in the presence of an electron-withdrawing group on the aromatic ring bearing a phenacyl azide moiety, using the optimized conditions.

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