Recent advances in the synthesis and applications  
of oxazolo[5,4-*d*]pyrimidines (microreview)

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**Introduction**

The target oxazolo[5,4-*d*]pyrimidines can be synthesized *via* two major strategic approaches, either *via* cyclization of pyrimidine derivatives resulted in the fused oxazole ring or by condensation of oxazole derivatives leading to fused pyrimidine rings. Oxazolo[5,4-*d*]pyrimidine scaffold is often used as a popular pharmacophore and structural element of wide range of bioactive compounds against diverse molecular targets, including potent kinases inhibitors,1 inhibitors of VEGFR-2,2 EDG-1,3 ACC24 proteins as well as immunosuppressive5 and an antiviral agents.6

**The synthesis from pyrimidine derivatives *via* formation of oxazole ring**

The most common method for the synthesis of oxazolo[5,4-*d*]pyrimidine scaffold is based on the dehydrative cyclisation

of *N*-(4-hydroxypyrimidin-5-yl)benzamides **2** using phosphorus oxychloride,7,5,8 phosphorus pentachloride9 or polyphosphoric (PPA) acid.1a In the usual manner required intermediate is prepared from appropriate 5-amino-6-hydroxypyrimidine and acid chloride or anhydride.1a,5,8 Recently, Gurenko and colleagues10 reported complementary approach starting from 2-aroylaminomalonodiamides **1**, which underwent condensation with ethyl formate in the presence of sodium ethoxide to form intermediates **2**, transformed in the next step to 2-aryl-7-chloro-oxazolo[5,4-*d*]pyrimidines **3** by boiling with phosphorus oxychloride. Finally, Kadereit *et all*9 described condensation between ethyl aroylaminomalonates **1** with amidines hydrochlorides, which resulted in formation of intermediates **4**, cyclised to the 2-aryl-5-alkyl-oxazolo[5,4-*d*]pyrimidin-7-one **5** by treatment with PCl5.



Condensation of 5-amino-6-hydroxypyrimidine (**6a**)with phenyl chlorothionocarbonate in the presence of pyridine, followed by treatment with pyrrolidine derivative, in the presence of TEA, lead after two steps to the carbothioamide **7**, which cyclized to the 2-pyrrolidine-oxazolo[5,4-*d*]pyrimidine **8** with silver nitrate in ammonia solution (cyclization yield not given).11 2-(4-chlorobenzyl)-5-amino-6-hydroxypyrimidine (**6b**)can be condensed with thiophosgene, which results in the formation of 2-mercapto-oxazolo[5,4-*d*]pyrimidine **9**.9



2-aryl-7-amino-oxazolo[5,4-*d*]pyrimidines **12** can also be synthesized from *N*-(4-chloropyrimidin-5-yl)benzamides **11** via copper-catalyzed intramolecular C-O bond formation leading to the oxazole ring.2a,12 Requested intermediates can be easily obtained from appropriate 5-amino-6-chloropyrimides **10** and acid chlorides. Cu-catalyzed cyclisation tolerates wide range of substituents at C4 position of pyrimidine ring including aminoaryl-, aminobenzyl- and aminophenetyl groups. Broad scope of applied (electron donating and electron withdrawing) substituents at Ar group allow the product synthesis from 35 to 90 % yield. Additionally, Branstetter reported,13 that cyclization of *N*-(4-chloropyrimidin-5-yl)phenylacetamide **13** to 2-benzyl-7-chloro-oxazolo[5,4-*d*]pyrimidine **14** can be also performed under catalyst-free conditions in the presence of cesium carbonate as a base, in hot acetonitrile, but the scope and limitations of such cyclisation were not reported.



**Violuric acid condensation**

Oxazolo[5,4-*d*]pyrimidine scaffold **1e** also can be obtained in the reaction between violuric acid **8** and triphenylmethylphosphonium bromide **9**, in the presence of lithium hydroxide followed by acidification of reaction mixture.15



**The synthesis from pyrimidine derivatives via formation of oxazole ring**

The target oxazolo[5,4-*d*]pyrimidines can also be synthesized from oxazole derivatives *via* formation of pyrimidine ring. 1,3-Oxazole-5-sulfonyl chlorides can be efficiently condensed with amidines, in the presence of triethylamine in anhydrous THF, giving two possible products depended on the applied sulfonyl chloride. Reaction of 4-cyano-1,3-oxazole-5-sulfonyl chlorides **19** with amidines **18** results in the formation of 7-amino-1,3-oxazolo[5,4-*d*]pyrimidines **20**,15 while condensation with methyl 2-aryl-5-chlorosulfonyl-1,3-oxazole-4-carboxylates **21** leads to the 6*H*,7*H*-[1,3]oxazolo[5,4-*d*]pyrimidin-7-ones **22**.16



**Condensation of 5-amino-4-cyano-1,3-oxazoles with formamidine, urea, formic acid, DMF-DMA/aniline and isothiocyanates**

5-Amino-4-cyano-1,3-oxazoles could serve as convenient substrates for the synthesis of oxazolo[5,4-*d*]pyrimidines and can be efficiently condensed with formamidine, urea and formic acid.18 Treatment of 5-amino-4-cyano-2-phenyl-1,3-oxazole (**12**) with dimethylformamide-dimethylacetal resulted in the intermediate dimethyliminoformamidine, which undergoes Dimroth rearrangement in the presence of anilines leading to *N*-phenyl-7-amino-1,3-oxazolo[5,4-*d*]pyrimidines **1h**.18 In the similar way condensation of **12** with aryl or alkylisocyanates, in the presence of DBU as a base, in anhydrous DMF, which led to the 7-amino oxazolo[5,4*-d*]pyrimidine-5(4*H*)-thiones **1i**.19



**From 5-aminooxazole-4-carboxylic acid ethyl esters by condensation  
with benzoyl isothiocyanates or *via* oxazolyliminophosphorane intermediates**

1,3-Oxazolo[5,4-*d*]pyrimidines can be synthesized from 5-aminooxazole-4-carboxylic acid ethyl esters (**13**) by condensation with acid isothiocyanates followed by basic cyclisation to pyrimidine ring with potassium hydroxide in boiling solvent.6 Obtained 5-mercaptooxazolo[5,4-*d*]pyrimidin-7(6*H*)-ones **1j** can be further functionalized by alkylation of thio group with alkyl or benzyl halides and thioether group could be finally exchange to the amine group after the treatment with methanolic ammonia. Another approach20 utilizes reaction between **13** and triphenyphosphine/hexachloroethane mixture leading to the iminophosphorane derivative **14**, which undergoes reaction with aryl isocyanate. Obtained carbodiimide intermediates **15** react with secondary amines, which led to the guanidines **16**, cyclised to the final products **1k** in the presence of sodium ethoxide in acetonitrile.



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