

Efficient and regioselective N-1 alkylation of 4-chloropyrazolo[3,4-*d*]pyrimidine

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Received 28 January 2007; revised 13 February 2007; accepted 23 February 2007

Available online 1 March 2007

Abstract—Efficient and N-1 selective alkylation of 4-chloropyrazolo[3,4-*d*]pyrimidine can be achieved when the heterocycle is reacted with alcohols under Mitsunobu conditions. The 1-alkyl-pyrazolo[3,4-*d*]pyrimidines formed can be functionalized further according to known methods, to give a variety of 1,4-disubstituted pyrazolo[3,4-*d*]pyrimidines. The first example of a palladium-catalyzed coupling reaction on a 4-halopyrazolo[3,4-*d*]pyrimidine is described.

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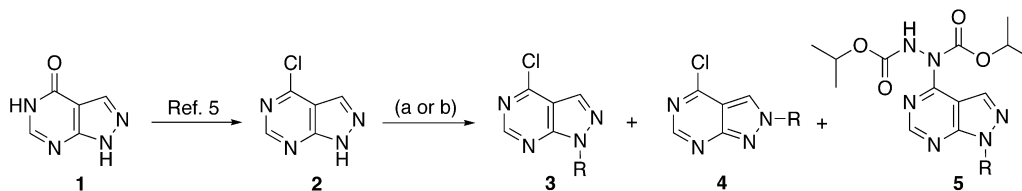
1,4-Disubstituted pyrazolo[3,4-*d*]pyrimidines have attracted attention as potential drugs or molecular tools. Some recently reported applications for this class of compounds are, for example, inhibition of various kinases,¹ inhibition of phosphodiesterase 9,² as well as inhibition of viral and bacterial growth.³ In most cases pyrazolo[3,4-*d*]pyrimidines are formed in several steps from a suitable pyrazole, or less frequently from a pyrimidine.⁴ However, allopurinol (**1**) (Scheme 1) is a commercially available pyrazolo[3,4-*d*]pyrimidine and thus an attractive starting point for the synthesis of 1,4-difunctionalized pyrazolo[3,4-*d*]pyrimidines. Allopurinol can readily be transformed into the corresponding 4-chloro derivative **2**,⁵ and chlorine in the pyrazolo[3,4-*d*]pyrimidine 4-position is readily displaced by *S*-, *N*- and *O*-nucleophiles or anions of active methylene reagents.^{4a} Carbon–carbon bond formation at the 4-position has also been achieved by metal-halogen exchange on 4-halopyrazolo[3,4-*d*]pyrimidines and subsequent trapping of the organometallic species with a carbonyl compound.⁶ The major challenge identified in transformation of allopurinol (**1**) into a 1,4-difunctionalized pyrazolo[3,4-*d*]pyrimidine was selective and efficient introduction of the N-1 substituent. This heterocyclic ring system is surprisingly unreactive under standard alkylation reactions employing an alkyl halide and a base. 1-Alkylated products have been obtained in reasonable yields when 4-halopyrazolo[3,4-*d*]pyrimidine

(**2**) was reacted with an alkyl iodide in the presence of cesium carbonate,⁷ but substantial amounts of the N-2 alkylated isomer were also formed and alkyl iodides are normally not as easily accessible as the corresponding chlorides or bromides. Structurally related heterocycles like purines⁸ and 3-deazapurines⁹ are often efficiently N-alkylated by the Mitsunobu reaction, an attractive methodology since alcohols instead of alkyl halides are used as alkylating agents. Hence we decided to study N-alkylation of 4-chloropyrazolo[3,4-*d*]pyrimidine (**2**) under Mitsunobu conditions.

Chloropyrazolo[3,4-*d*]pyrimidine **2** was reacted with alcohols in the presence of triphenylphosphine and DIAD (Scheme 1, Table 1).¹⁰

When compound **2** was alkylated with *n*-butanol under Mitsunobu conditions, 1-butyl-4-chloropyrazolo[3,4-*d*]pyrimidine **3a** was isolated as the only product in 77% yield. However, formation of other products in minor amounts, co-eluting with the reduced form of DIAD or triphenylphosphine oxide formed during the reaction, cannot be excluded. The presence of these co-products also precluded a thorough study of products formed by NMR spectroscopy of the crude product. In reactions with several other alcohols, minor amounts of the N-2 alkylated isomer **4** were isolated, but the selectivity towards N-1 alkylation was generally high. The Mitsunobu protocol compared favourably with the previously published N-alkylation employing alkyl iodide and cesium carbonate,⁷ which gave a mixture of N-1 and N-2 alkylated products and a low yield

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Scheme 1. Reagents and conditions: (a) ROH, PPh₃, DIAD, THF; (b) RI, Cs₂CO₃, DMF.

Table 1. N-Alkylation of 4-chloropyrazolo[3,4-*d*]pyrimidine (**2**)

R	Method ^a	Temperature (°C)	Time (h)	Yield (%) 3	Yield (%) 4	Yield (%) 5
<i>n</i> -Bu	a	0–rt	6	77, 3a	— ^b	— ^b
<i>n</i> -Bu	b	0	2	26, 3a	11, 4a	—
<i>n</i> -Hex	a	0	3	72, 3b	— ^b	4 , 5b
CH ₃ OCH ₂ CH ₂	a	0	2.5	59, 3c	— ^b	— ^b
<i>i</i> -Bu	a	0–rt	6	72, 3d	— ^b	— ^b
<i>c</i> -Hex–CH ₂	a	0	2.5	65, 3e	— ^b	10, 5e
(2-Tetrahydrofuryl)CH ₂	a	0	3	39, 3f	— ^b	— ^b
<i>p</i> -CH ₃ O–C ₆ H ₄ –CH ₂	a	0–rt	6	47, 3g	— ^c	— ^c
<i>p</i> -CH ₃ O–C ₆ H ₄ –CH ₂	b	0	3	32, 3g	<8, 4g ^d	—
CH ₂ =CHCH ₂	a	0	3	62, 3h	17, 4h	7, 5h
HC≡CCH ₂	a	0	0.75	48, 3i	— ^b	8, 5i
HC≡CCH ₂ CH ₂	a	0	0.75	64, 3j	6, 4j	15, 5j
<i>i</i> -Pr	a	0	3.5	60, 3k	— ^b	13, 5k
<i>c</i> -Pent	a	0	1	73, 3l	3, 4l	11, 5l
<i>c</i> -Hex	a	Δ	6	21, 3m	— ^b	— ^b

^a See Scheme 1.

^b Not isolated.

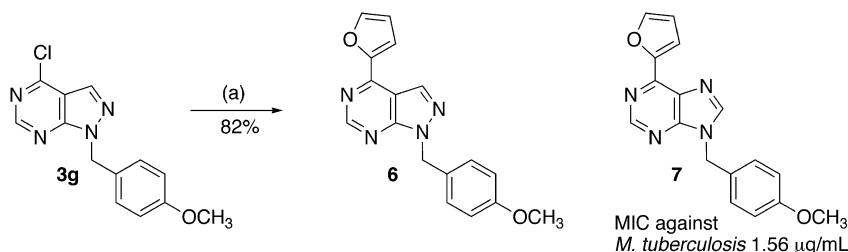
^c A ca. 3:1 mixture of **4g** and **5g** was isolated indicating the formation of ca 20% of **4g**.

^d Not isolated pure.

of the desired isomer **3a**. The identification of isomers **3** and **4** was mainly based on ¹³C NMR spectroscopy as described previously.⁷

As can be seen from Table 1, a variety of alcohols, including allylic, propargylic and benzylic alcohols, reacted readily with the chloropyrazolo[3,4-*d*]pyrimidine **2** to give 1-substituted compounds **3**, generally with high regioselectivity and in good yields compared to existing methodology. The lowest regioselectivity was obtained in the introduction of the *p*-methoxybenzyl group, but compound **3g** was still isolated in better yield from the Mitsunobu reaction than by alkylation with *p*-methoxybenzyl iodide, a commercially unavailable iodide.¹¹ Also, secondary alkyls could be introduced, but the reaction with cyclohexanol required reflux temperature and the yield of product **3m** was rather modest. The inferior performance of cyclohexanol in Mitsunobu reactions has been reported before.¹²

As mentioned above, 4-chloropyrazolo[3,4-*d*]pyrimidines are prone to nucleophilic displacement of the halogen,^{4a} and several nucleophilic species are present in the reaction mixture during the Mitsunobu reaction. In some cases we isolated minor amounts of compounds **5** containing a DIAD derived substituent at C-4, but we never isolated any 4-alkoxy-pyrazolo[3,4-*d*]pyrimidines which theoretically could have been formed from nucleophilic attack of the alcohols used. Once formed, 9-alkyl-4-chloropyrazolo[3,4-*d*]pyrimidines **3** may easily be derivatized further by nucleophilic substitutions to give a variety of 1,4-disubstituted pyrazolo[3,4-*d*]pyrimidines as discussed above. We chose, to the best of our knowledge for the first time, to subject a 4-chloropyrazolo[3,4-*d*]pyrimidine to a palladium catalyzed coupling reaction. Stille coupling between compound **3g** and (2-furyl)tributyltin gave the furyl derivative **6** in high yield (Scheme 2). Compound **6** is an isomer of the previously reported



Scheme 2. Reagents and conditions: (a) (2-furyl)tributyltin, (Ph₃P)₂PdCl₂, DMF, 90 °C.

antimycobacterial purine **7**.¹³ Biological activity of **6** will be published elsewhere.

Acknowledgement

The Norwegian Research Council is gratefully acknowledged for partial financing of the Bruker Avance instruments used in this study.

Supplementary data

Spectroscopic data for all new compounds and a procedure for the synthesis of compound **6**, can be found in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.116.

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