



Acyl radical insertion for the direct formation of new seven-substituted pterin analogs

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ABSTRACT

A variety of pterin molecules were synthesized via an under-utilized acyl radical insertion, using aldehydes and α -keto esters as the acyl source. These reactions gave complete regioselectivity for the 7-isomer, with reaction times ranging in minutes, often with instantaneous product precipitation. This approach led to the construction of new pterin analogs inaccessible via traditional Friedel–Crafts acylation. The compounds were characterized by NMR spectroscopy and high-resolution mass spectroscopy.

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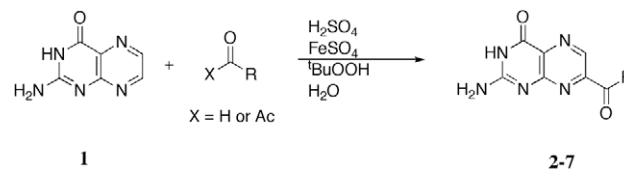
Pterins have been shown to be a noteworthy lead in the search for Ricin A chain inhibitors.¹ In this context, we have explored different routes to pterin libraries, particularly those which remove extraneous steps often needed to circumvent pterins' insolubility and poor reactivity. As with other diazoaromatic compounds, such as pyrazines, direct substitution by electrophiles is not a viable reaction for pterins, as a result of these being so π -electron deficient.^{2,3} For this reason, the formation of acylpterins is typically done through oxidation of alkyl side-chains to carboxylates or alcohols.^{4,5} Taylor developed a method for forming isomerically pure alkyl pterins, though it requires a multi-step construction of the ring.⁶ Methods exist for the formation of isomerically enriched alkyl pterins through a traditional one-step condensation, but the formation of the undesirable isomer is still observed.⁵ Furthermore, due to the poor solubility of pterins, isolation of the desired isomer can be difficult, often requiring further modifications.^{5,7}

Direct acylation of heteroaromatic bases was first shown by Caronna, whereby an aldehyde is allowed to react with a peroxide in the presence of iron sulfate, generating an acyl radical which can insert onto the protonated heterocyclic species.⁸ This reaction has been performed on a variety of simple heterocycles, and has also been shown to proceed with α -keto esters as the acyl source.^{2,9,10} Substituent-directing effects have been studied, and it was found that groups which are electron withdrawing by resonance and inductive effects direct to the para position.¹¹ As related to pterins, these directing effects would regioselectively provide the 7-isomer. This reaction has previously been utilized on molecules containing the general pteridine substructure, and it was indeed found that when both heteroaromatic positions are available, only the 7-isomer is formed, while placement of electron-donating substituents on the 7-position allowed access to the 6-isomer.^{12–14} However, these pteridine analogs often had several preemptive

modifications and all required post-reaction substituent conversion to arrive at the pterin.^{12–14} It thus follows that the overall yield of the desired pterins would suffer from these additional steps.

We report here the use of peroxide and iron sulfate for the direct one-step formation of a variety of pterins, starting simply from pterin (**1**). As shown, aldehydes gave rise to acylpterins (**2–5**), and α -keto esters gave rise to pterin esters (**6–7**).

The general procedure for the reaction depicted in Scheme 1 involves suspending pterin (**1**) in 50–60 mL water, and adding 5–6 mL concentrated sulfuric acid along with 2 equiv iron sulfate. Separately, 5 equiv of the aldehyde and 2 equiv of ^tbutylperoxide were mixed together, with cooling, and then added dropwise to the reaction. In the cases where esters or amides inserted onto the pterin, the product precipitated out instantaneously. In instances where precipitation was not observed, the addition of a small amount of ammonium hydroxide afforded the desired product as a precipitate. The results are summarized in Table 1. The



Scheme 1. Acyl radical addition to pterin.

Table 1

Entry	Acyl source	Time (min)	Product	% Yield
2	Acetaldehyde	10	R = CH ₃	42
3	Propionaldehyde	10	R = CH ₂ CH ₃	37
4	Formamide	3	R = NH ₂	31
5	Anisaldehyde	10	R = C ₆ H ₄ OCH ₃	22
6	Methyl pyruvate	2	R = OCH ₃	48
7	Ethyl pyruvate	3	R = OCH ₂ CH ₃	39

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moderate yields are consistent with results seen previously for unsubstituted pteridines, and the lower yield seen with anisaldehyde is attributed to poor solubility in water.¹² Longer reaction times did not yield higher product conversion.

In summary, we have used an acyl radical reaction for the fast, direct, and regiospecific construction of a number of pterin compounds, recoverable by simple filtration. Using this reaction directly on pterin removes the need for substituent conversions, which would affect the overall yield.

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Supplementary data

Supplementary data (general experimental procedure, NMR and MS data) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.03.008](https://doi.org/10.1016/j.tetlet.2010.03.008).

References and notes

1. Yan, X.; Hollis, T.; Svinth, M.; Day, P.; Monzingo, A. F.; Milne, G. W. A.; Robertus, J. D. *J. Mol. Biol.* **1997**, *266*, 1043.
2. Houminer, Y.; Southwick, E. W.; Williams, D. L. *J. Heterocycl. Chem.* **1986**, *23*, 497.
3. Hurst, D. T. In *Science of Synthesis*, Houben-Weyl, Ed.; Wiley, 1997; Vol. E9, p 299.
4. Pfeleiderer, W.; Zondler, H.; Mengel, R. *Justus Liebigs Ann. Chem.* **1970**, *741*, 64.
5. Waring, P.; Armarego, W. L. F. *Aust. J. Chem.* **1985**, *38*, 629.
6. Taylor, E. C.; Perlman, K. L.; Sword, I. P.; Sequin-Frey, M.; Jacobi, P. A. *J. Am. Chem. Soc.* **1973**, *95*, 6407.
7. Taylor, E. C.; Otiv, S. R.; Durucasu, I. *Heterocycles* **1993**, *36*, 1883.
8. Caronna, T.; Gardini, G. P.; Minisci, F. *Chem. Commun. (London)* **1969**, 201.
9. Caronna, T.; Fronza, G.; Minisci, F.; Porta, O. *J. Chem. Soc., Perkin Trans. 2* **1972**, 2035.
10. Heinisch, G.; Loetsch, G. *Tetrahedron* **1986**, *42*, 5973.
11. Houminer, Y.; Southwick, E. W.; Williams, D. L. *J. Org. Chem.* **1989**, *54*, 640.
12. Baur, R.; Kleiner, E.; Pfeleiderer, W. *Liebigs Ann. Chem.* **1984**, 1798.
13. Baur, R.; Sugimoto, T.; Pfeleiderer, W. *Helv. Chim. Acta* **1988**, *71*, 531.
14. Doering, T.; Boruah, R. C.; Pfeleiderer, W. *Pteridines* **2004**, *15*, 129.