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An efficient synthesis of phenanthro-fused thiazoles by a non-phenolic oxidative coupling procedure of 4,5-diarylthiazoles

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Abstract. A concise synthesis of the title compounds **6** is accomplished in high overall yield in a two step process starting from bromoketone **4**. A thiazole ring formation and a non-phenolic oxidative coupling reaction using PIFA are features of the described synthesis. An exploration of the electronic requirements and the regioselectivity of the cyclization is also presented.

Very recently, a short and efficient synthesis of a series of phenanthro[9,10-*d*]pyrimidines *via* a Stille coupling reaction between suitably substituted 4,5-diarylpyrimidines was published.[1a] The importance of this type of structure relies on its already known properties and its potential pharmacological applications,[2] which are a consequence of the planarity of the phenanthrene skeleton in conjunction with the nature of the fused heterocycle (pyrimidines or others). Syntheses of a number of different natural and non-natural phenanthro-fused heterocycles have been reported.[3]

In this *Letter* an efficient synthesis of 2,3,6,7-tetramethoxyphenanthro[9,10-*d*]thiazoles **6** by a non-phenolic oxidative coupling reaction of the corresponding 4,5-diarylthiazole precursors **5** is presented. Additionally, after optimization of the oxidative coupling conditions, a series of the substrates **5** was prepared in order to explore the electronic requirements and the regioselectivity of the process when unsymmetrically substituted starting materials are employed.

There are two reasons to focus on the thiazole heterocycle. Firstly, the thiazole moiety is present in a number of important natural products (*epothilone*,[4a] *althiomycin*,[4b] *bistramide C*,[4c] *sulfomycin I*[4d]) in antibiotics (*cystothiazole*),[5] in columnar mesogenic compounds (benzotristhiazole)[6] and in cyclopeptide alkaloids (*ulithiacyclamide, ascidiacyclamide*),[7] *inter alia*. Secondly, the behaviour of the thiazole system under oxidative coupling conditions remains unknown.

In order to optimize the reaction conditions for the synthesis of phenanthro-fused thiazoles, we first tried to adapt our previously employed strategy[1b] to our new synthetic purpose and, thus, it was found that treatment of enaminoketone **1** with 1,2-aminoethanethiol[8] readily afforded derivative **3** by an amine exchange process.[9] However, the desired intramolecular ring closure to afford an *N,S*-containing seven-membered heterocycle **2b** could never be accomplished, probably due to the lack of aromaticity in the final hetero-ring (see Scheme 1).

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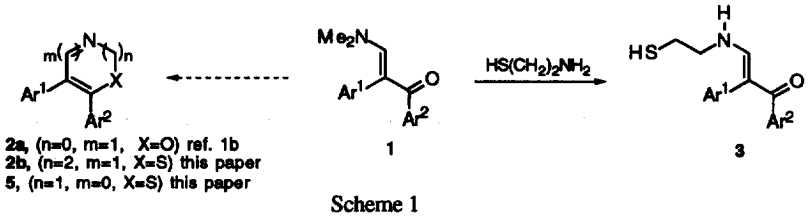
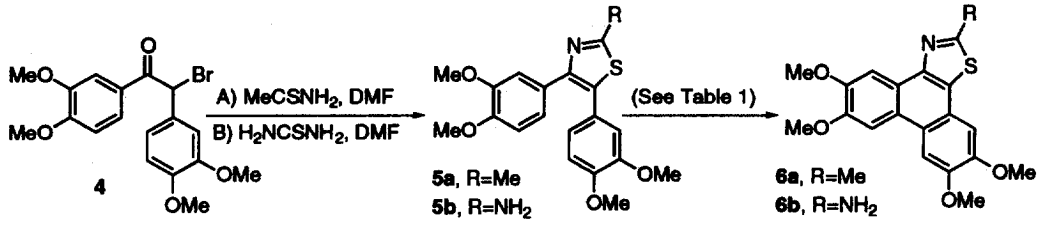


Scheme 1

Therefore, the alternative protocol described in Scheme 2 was developed. Thus, bromoketone **4**, easily accessible from the corresponding deoxybenzoin in high yield (>80%) employing either NBS in CCl_4 or Br_2 in refluxing chloroform, was treated separately with thioacetamide and thiourea, both in DMF, to afford the 4,5-diarylthiazoles **5a** and **5b**, respectively, in excellent yields (>90%). The lower temperature (60 °C *vs* r.t.) and shorter reaction time (12h *vs* 6h) needed in the latter case could be accepted as a consequence of the higher reactivity of thiourea under the reaction conditions.



Scheme 2

At this point of the research, thiazole **5a** was selected to optimize the final coupling step. For that purpose, different oxidative conditions were evaluated and the results summarized in Table 1 were obtained. By inspection of these results, the robustness of the thiazole ring was verified in all cases. Nevertheless, in spite of the clean transformation observed when Ru(IV),[10] Fe(III)[11] and V(V)[12] reagents were used (entries 1-5), significant amounts of unreacted starting material were recovered even though ultrasonic assisted stirring was employed (entries 2 and 4). In order to find a better coupling reagent, and to avoid the use of highly toxic oxidants, the use of phenyliodine(III) *bis*(trifluoroacetate) reagent (PIFA) was examined.[13] In this case (entry 6), not only was a clean transformation observed, but the conversion was also dramatically improved, affording the tetracyclic objective **6a** in an excellent yield.

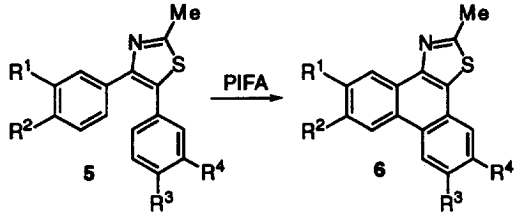
PIFA was also the reagent chosen to execute successfully the transformation of the aminothiazole **5b** into **6b** (entry 7). In fact, while treatment with $FeCl_3$ yielded the target coupling product with a very low conversion (15%), the conditions described in entries 1, 2 and 5 failed, giving rise to complex mixtures of unidentified products.

Table 1. Oxidative coupling assays performed on thiazoles **5a** and **5b**.

Entry	Reaction Conditions	Yield (%)
1	RuO_2/TFA/TFAA/BF_3OEt_2/CH_2Cl_2/r.t.	40[a]
2	RuO_2/TFA/TFAA/BF_3OEt_2/CH_2Cl_2/r.t./sonication	45[a]
3	$FeCl_3$/CH_2Cl_2/r.t.	35[a]
4	$FeCl_3$/CH_2Cl_2/r.t./sonication	37[a]
5	VOF_3/TFAA/CH_2Cl_2/r.t.	20[a]
6	PIFA/BF_3OEt_2/CH_2Cl_2/-20 °C	81[a]
7	PIFA/BF_3OEt_2/CH_2Cl_2/r.t.	83[b]

[a]Yield of isolated **6a**. No other byproduct, apart from starting material, was detected. [b]Yield of **6b** from **5b**.

Once the optimized conditions for the cyclization step were established, a series of substrates **5** was prepared[14] in order to study the electronic requirements and regioselectivity of this process.



5a/6a, R^1=R^2=R^3=R^4=OMe (81%)
5c/6c, R^1=R^2=R^3=R^4=H (0%)
5d/6d, R^1=R^2=OMe, R^3=R^4=H (74%)
5e/6e, R^1=R^2=R^4=OMe, R^3=H (77%)
5f/6f, R^1=R^2=OMe, R^3=NO_2, R^4=H (72%)
5g/6g, R^1=OMe, R^2=R^3=R^4=H (<5%)

Scheme 3

From the results obtained the following conclusions can be proposed: 1) activation with electron-donating groups is needed in at least one of the rings. 2) if only one methoxy group is present, the yield decreases dramatically (less than 5% for **6g**);[15] 3) the reaction takes place in good yield (72-81%) provided two methoxy groups are present in one of the rings (**6a**, **6d**, **6e**, **6f**); 4) finally, no other regioisomers, apart from the ones described in Scheme 3, were detected. Compounds **6a**, **6d**, **6e** and **6f** were obtained as unique regioisomers when one methoxy group (**6d**, **6f**) or two methoxy groups (**6a**, **6e**) were located *para* to the cyclization point(s).

In summary, a novel synthesis of new phenanthro-fused thiazole derivatives **6** starting from α-bromodeoxybenzoins **4** has been described.[16] The scope, limitations and regioselectivity of the cyclization step is presented. The crucial non-phenolic coupling step has been accomplished from very accessible precursors. The mild conditions employed are compatible with the thiazole system and no protection for the free amino group in derivative **5b** is required. Because of its simplicity and high overall yield, we envisage tremendous potential for the preparation of a series of different heterocyclic analogues by employing our synthetic strategy, a field of research which, at the moment, is under progress.

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8. 1,2-aminoethanethiol is the simplest commercially available aminothiol.
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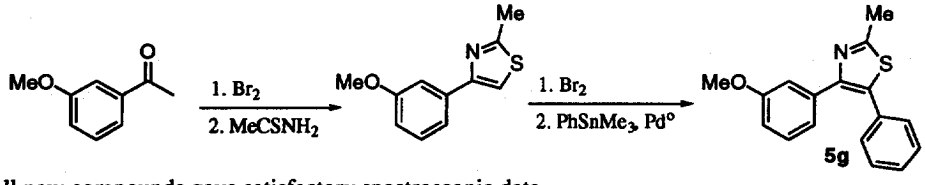
14. Following the general procedure outlined in the text, 4,5-diarylthiazoles **5c**, **5d**, **5e** and **5f** were regioselectively prepared from **4c**, **4d**, **4e** and **4f** in excellent yields: 91%, 94%, 89% and 92% respectively. In each case the assigned regiochemistry was based on previous reports. See for example: Ramana, M. M. V.; Dubhashi, D. S.; D´Souza, J. J. *J. Chem. Research (S)* **1998**, 496-496 and references cited therein.
15. Compound **6g** was detected, but not isolated, by MS. The actual structure (*a priori* two regioisomers can be formed) could not be established. Precursor **5g** had to be prepared by an alternative route (shown below) since the Friedel-Crafts acylation approach has severe limitations: i) highly activated rings are needed on one of the aromatic rings; ii) mixture of isomers can be obtained; iii) the availability of commercial precursors (arylacetic acids or arylacetyl halides) is small.
Synthetic and experimental details of these two complementary syntheses will be published elsewhere.



16. All new compounds gave satisfactory spectroscopic data.