Novel applications of the hypervalent iodine chemistry. Synthesis of thiazolo-fused quinolinones

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Abstract

A synthesis of thiazolo[5,4-*c*]quinolinone derivatives featuring the use of two different hypervalent iodine reagents has been achieved starting from ethyl benzoylacetate in an efficient way. Hydroxy(tosyloxy)phenyliodine (HITB, Koser´s reagent) has been employed to functionalize the starting β-ketoester **4**, and phenyliodine(III)*bis*(trifluoroacetate) (PIFA) to perform a ring closure reaction on the corresponding *N*-methoxyamides **9** and **14**.

Keywords: Hypervalent iodine, PIFA; HITB, quinoline, thiazole, cyclization

Introduction

In recent years our group has been concerned with the development of the hypervalent iodine chemistry. In particular, we have reported the superior behavior of PIFA as a biaryl coupling reagent, over other metallic oxidants, in the preparation of polycyclic heterocycles such as phenanthrenes,[1] phenanthrenoids[2] and benzo[*c*]phenanthridines.[3] The clean transformations achieved, the mild conditions employed, and the low toxicity associated to it, prompted us to include PIFA in our synthetic plans.

Thus, we next focused our attention in the known ability of PIFA to generate *N*-acylnitrenium ions from *N*-alkoxyamides[4] which, eventually, could be trapped, intramolecularly in our case, by arene rings to afford the quinoline skeleton in a simple way (see Scheme 1).
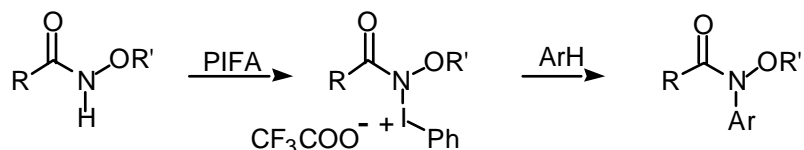
Scheme 1

In this context, we considered that the pharmacological versatility of quinoline derivatives[5] could be modified, or even enhanced, in their heterocycle-fused analogues.[6] In fact, the synthesis and the activity of a number of natural products with fused quinoline heterocyclic skeletons have been reported.[7] In particular, we considered that the thiazole moiety, which is present in a number of important natural products (*epothilone*,[8] *althiomycin*,[9] *bistramide* C,[10] *sulfomycin* I[11]), in antibiotics (*cystothiazole*[12]) and, notably, in thiamine (vitamin B) *inter alia*, would be an interesting and promising substructure to be included in our target molecules.[13]

Thus, in this paper we want to show a simple and efficient synthesis of thiazolo[5,4-*c*]quinolin-4-ones of type **1** from β-ketoesters **3** following the retrosynthetic analysis depicted in Scheme 2.
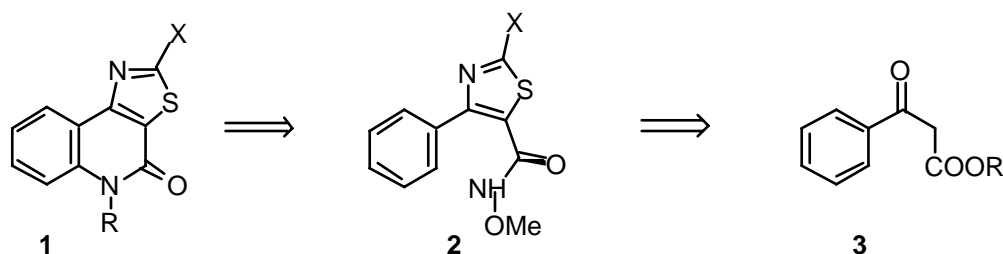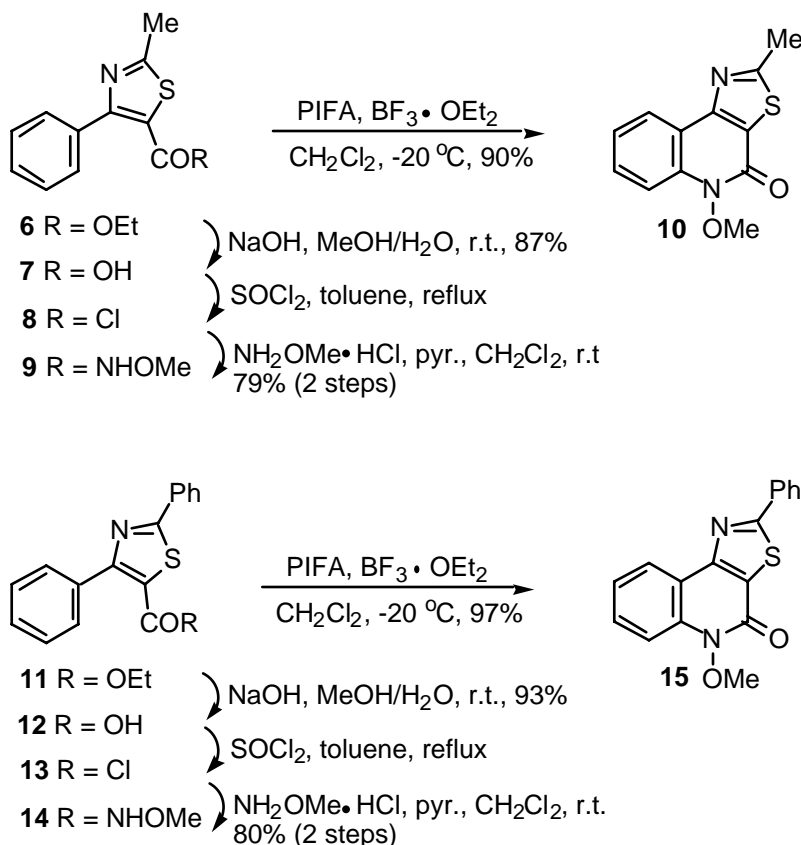

Scheme 2

Results and Discussion

The construction of the substituted thiazole ring started, as shown in Scheme 3, with the HITB-mediated oxytosylation of commercially available β-ketoester **4**[14] followed by application of the Hantzsch conditions on the resulting ester **5**. α-Tosyloxy substituted ketones, as **5**, have encountered a wide application in organic synthesis as alternative precursors to the corresponding halo-derivatives but without their unpleasant lachrymose properties.[15] Thus, heating ester **5** in DMF in the presence of thioacetamide or thiobenzamide afforded thiazoles **6** and **11**, respectively, in very good yields (see Scheme 3).
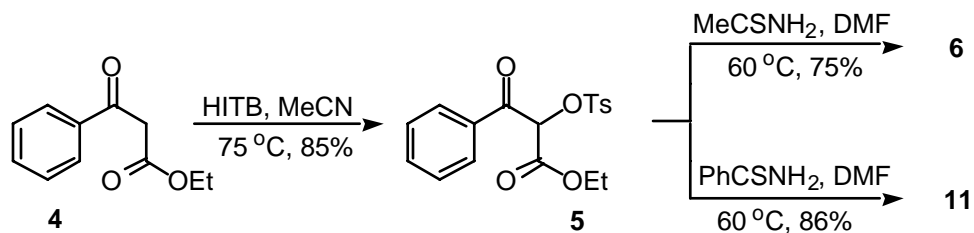
Scheme 3

At this point (see Scheme 4), basic hydrolysis of the ester groups and subsequent activation of the resulting free carboxylic acids **7** and **12** with thionyl chloride afforded the corresponding acyl chlorides **8** and **13** which, without isolation, were treated following standard procedures with methoxylamine to yield the required *N*-methoxyamides **9** and **14**, respectively. Kikugawa had previously employed this kind of precursor in an electrophilic aromatic substitution reaction, which involved a *N*-chlorination step with t-BuOCl and oxidative cyclization using silver or zinc salts.[16] Similarly, Cherest and Lusinchi employed ferric chloride with the same purpose.[17] Later, it was found[4] that limitations associated with these protocols (i. e. solubility of silver salts or undesired aromatic chlorination) could be overcome by using PIFA as the cyclization reagent in a single step. Following this strategy, the prepared amides **9** and **14** were treated with the cyclization reagent under optimized experimental conditions to afford the desired thiazoloquinolinones **10** and **15** in 90% and 97% yield, respectively. The same products were obtained when TFA was employed as an alternative to boron trifluoride but with lower yields and longer reaction times.

Scheme 4

In conclusion, the iodine (III)-mediated preparation of thiazolo[5,4-*c*]quinolin-4-ones has been described. The validity of the employed protocol in the synthesis of other quinolinone fused heterocycles, as well as the scope of substituents in the aromatic moiety of the quinolinone nucleus ring is currently under study.

Experimental Section[18]

Typical procedure for the Hantzsch cyclization. Synthesis of 5-ethoxycarbonyl-2-methyl-4-phenylthiazole (6)

A solution of ester **5**[14] (1 g, 2.76 mmol) and thioacetamide (0.31 g, 4.14 mmol) in DMF (10 mL) was stirred at 60 ^{o}C for 24 h (48 h for **11**). After reaching rt, EtOAc (20 mL) was added and washed with H_2O (3x10 mL). The aqueous layer was dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum. The resulting mixture was column chromatographed (Hex/AcOEt, 8/2) to afford an oil which was crystallized from hexanes (75%). mp 32–35 ^{o}C (Hexanes); ^{1}H-NMR (CDCl$_3$) 1.26 (t, *J*= 7.1, 3H, CH$_2$-C$\underline{H}_3$), 2.73 (s, 3H, CH$_3$), 4.25 (q, *J* =7.1, 2H, CH$_2$), 7.41-7.43 (m, 3H, H$_{arom}$), 7.70-7.73 (m, 2H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$) 13.7, 19.0,

60.9, 122.0, 127.3, 128.6, 129.4, 133.7, 159.3, 160.9, 168.5; IR (KBr) 1721 cm^{-1}. Anal. Calcd for C$_{13}$H$_{13}$NO$_2$S: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.33; H, 5.59; N, 5.40.

2,4-Diphenyl-5-ethoxycarbonylthiazole (11). According to the typical procedure thiazole **11** was obtained from ester **5** in 86% yield as a yellowish solid. mp 103–105 ^{o}C (Et$_2$O); ^{1}H-NMR (CDCl$_3$) 1.33 (t, J =7.1, 3H, CH$_2$-C$\underline{H}_3$), 4.32 (q, J =7.1, 2H, CH$_2$), 7.46-7.50 (m, 6H, H$_{arom}$), 7.86-7.90 (m, 2H, H$_{arom}$), 8.04-8.08 (m, 2H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$) 14.0, 61.4, 122.2, 126.7, 127.6, 128.9, 129.0, 129.8, 131.0, 132.7, 134.0, 160.6, 161.4, 169.6; IR (KBr) 1721 cm^{-1}. Anal. Calcd for C$_{18}$H$_{15}$NO$_2$S: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.63; H, 4.59; N, 4.33.

Typical procedure for the hydrolysis of esters 6 and 11. Synthesis of 5-carboxy-2-methyl-4-phenylthiazole (7)

Over a solution of ester **6** (0.53 g, 2.14 mmol) in MeOH (20 mL), NaOH (0.52 g, 13 mmol) and 2-5 mL of water was added. The mixture was stirred at rt until total consumption of the starting material (1 d). Then, HCl (5% ac.) was added and the mixture was extracted with EtOAc (3 x 10 mL). The aqueous layer was dried over Na$_2$SO$_4$, filtered and the solvent was evaporated under vacuum. The resulting mixture was column chromatographed (Hex/AcOEt, 2/8) to afford carboxylic acid **7** as a white solid which was crystallized from hexanes (87%). mp 186–187 ^{o}C (Hexanes); ^{1}H-NMR (DMSO) 2.69 (s, 3H, CH$_3$), 7.39-7.41 (m, 3H, H$_{arom}$), 7.69-7.70 (m, 2H, H$_{arom}$), 11.49 (sa, 1H, COOH); ^{13}C-NMR (DMSO) 19.2, 123.6, 127.8, 128.9, 130.0, 134.2, 158.2, 162.4, 168.7; IR (KBr) 3409, 1647 cm^{-1}. Anal. Calcd for C$_{11}$H$_9$NO$_2$S: C, 60.26; H, 4.14; N, 6.39. Found: C, 60.33; H, 4.39; N, 6.43.

2,4-Diphenyl-5-carboxythiazole (12). According to the typical procedure carboxylic acid **12** was obtained from ester **11** in 93% yield as a white solid. mp 202–204 ^{o}C (MeOH); ^{1}H-NMR (DMSO) 7.44-7.47 (m, 3H, H$_{arom}$), 7.53-7.55 (m, 3H, H$_{arom}$), 7.78-7.82 (m, 2H, H$_{arom}$), 8.01-8.05 (m, 2H, H$_{arom}$), 13.49 (sa, 1H, COOH); ^{13}C-NMR (DMSO) 124.0, 126.8, 127.8, 129.1, 129.5, 130.1, 131.5, 132.4, 134.2, 159.3, 162.4, 168.6; IR (KBr) 3000-2000, 1660 cm^{-1}. Anal. Calcd for C$_{16}$H$_{11}$NO$_2$S: C, 68.31; H, 3.94; N, 4.98. Found: C, 68.53; H, 4.00; N, 4.73.

Typical procedure for the synthesis of amides 9 and 14. Synthesis of 5-(N-methoxycarbamoyl)-2-methyl-4-phenylthiazole (9)

Thionyl chloride (0.15 mL, 2.05 mmol) was added to a solution of the carboxylic acid **7** (0.3 g, 1.37 mmol) in CH$_2$Cl$_2$ (10 mL). The mixture was heated at reflux for 4 h. Removal of solvent *in vacuo* gave the corresponding aroyl chloride **8** as a residue which, without isolation, was dissolved again in CH$_2$Cl$_2$ (15 mL). To this solution, hydroxylamine (HCl salt) (0.12 g, 1.51 mmol) and pyridine (0.27 mL, 3.30 mmol) was added at 0 ºC, and the mixture was stirred at rt until the conversion was complete. Then, the solution was washed with saturated CuSO$_4$, the organic layer was dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The residue was column chromatographed (Hex/EtOAc, 3/7) and the resulting amide **9** was crystallized from hexanes as a pale brown solid. mp 154–155 ^{o}C (Hexanes); ^{1}H-NMR (CDCl$_3$) 2.74 (s, 3H, CH$_3$), 3.72 (s, 3H, OCH$_3$), 7.47-7.51 (m, 3H, H$_{arom}$), 7.59-7.65 (m, 2H, H$_{arom}$), 8.15 (s, 1H, NH); ^{13}C-NMR (CDCl$_3$)

19.2, 64.2, 128.8, 129.4, 124.8, 133.4, 154.3, 160.1, 168.2; IR (KBr) 3113, 1670 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.26; H, 4.69; N, 11.43.

2,4-Diphenyl-5-(*N*-methoxycarbamoyl)thiazole (14). According to the typical procedure amide **14** was obtained from acid **12** in 80% yield as a pale brown solid. mp 145–147 ^{o}C (Et$_2$O); ^{1}H-NMR (CDCl$_3$) 3.72 (s, 3H, OCH$_3$), 7.40-7.53 (m, 6H, H$_{arom}$), 7.69-7.71 (m, 2H, H$_{arom}$), 7.94-8.00 (m, 2H, H$_{arom}$), 8.47 (sa, 1H, NH); ^{13}C-NMR (CDCl$_3$) 64.3, 124.9, 126.7, 128.9, 129.6, 130.9, 132.5, 133.6, 155.4, 160.2, 169.4; IR (KBr) 3158, 1662 cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.46; H, 4.69; N, 9.33.

Typical procedure for the cyclization of amides 9 and 14. Synthesis of *N*-methoxy-2-methylthiazolo[5,4-*c*]quinolin-4-one (10)

A solution of PIFA (139 mg, 0.32 mmol) and BF$_3$·OEt$_2$ (0.08 mL, 0.65 mmol) in 8 mL of CH$_2$Cl$_2$ was added at – 20 ºC to a solution of amide **9** (53 mg, 0.21 mmol) in 5 mL of the same solvent. The mixture was stirred at the same temperature during 20 min, washed with 10% aqueous NaHCO$_3$ and dried over Na$_2$SO$_4$. Then, the solvent was evaporated and the residual oil was column chromatographed (Hexanes/EtOAc, 6:4) and crystallized from hexanes to afford pure quinolinone **10** (47 mg, 90%) as a yellowish solid. mp 180–182 ^{o}C (Hexanes); ^{1}H-NMR (CDCl$_3$) 2.91 (s, 3H, CH$_3$), 4.15 (s, 3H, OCH$_3$), 7.37-7.44 (m, 1H, H$_{arom}$), 7.62-7.73 (m, 2H, H$_{arom}$), 8.40-8.43 (m, 1H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$) 20.2, 63.2, 112.4, 116.5, 123.3, 124.7, 130.4, 136.6, 153.5, 154.4, 173.6; IR (KBr) 1656 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.73; H, 4.10; N, 11.15.

N-Methoxy-2-phenylthiazolo[5,4-*c*]quinolin-4-one (15). According to the typical procedure quinolinone **15** was obtained from amide **14** in 97% yield as a white solid. mp 183–185 ^{o}C (Et$_2$O); ^{1}H-NMR (CDCl$_3$) 4.19 (s, 3H, OCH$_3$), 7.43 (t, *J* = 7.9, 1H, H$_{arom}$), 7.53-7.55 (m, 3H, H$_{arom}$), 7.64-7.75 (m, 2H, H$_{arom}$), 8.14-8.17 (m, 2H, H$_{arom}$), 8.56 (d, J= 7.9, 1H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$) 63.2, 112.3, 116.6, 123.2, 124.5, 124.8, 127.2, 128.9, 130.3, 131.5, 132.5, 136.6, 153.5, 155.0, 174.0; IR (KBr) 1668 cm^{-1}. Anal. Calcd for $C_{17}H_{12}N_2O_2S$: C, 66.22; H, 3.92; N, 9.08. Found: C, 66.33; H, 3.79; N, 9.10.

Acknowledgements

References and Notes

1. Moreno, I.; Tellitu, I.; SanMartín, R.; Badía, D.; Carrillo, M. L.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 5067.

2. Moreno, I.; Tellitu, I.; SanMartín, R.; Domínguez, E. *Synlett* **2001**, 1161.

3. Moreno, I.; Tellitu, I.; Etayo, J.; Domínguez, E.; SanMartín, R. *Tetrahedron* **2001**, *57*, 5403.

4. (a) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581. (b) Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem.* **1997**, *62*, 6582.

5. See for example: (a) Desos, P.; Lepagnol, J. M.; Morain, P.; Lestage, P.; Cordi, A. A. *J. Med. Chem.* **1996**, *39*, 197. (b) Oshiro, Y.; Sakurai, Yoji; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Miwa, T.; Nishi, T. *J. Med. Chem.* **2000**, *43*, 177.

6. See for example: (a) Mekheimer, R. A. *Synthesis* **2000**, 2078. (b) Mekheimer, R. A.; Ahmed, E. K.; El-Fahham, H. A.; Kamel, L. H. *Synthesis* **2001**, 97. and references cited therein.

7. Recent examples of natural heterocycle-fused quinolines and quinolinones can be found in: (a) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 603. (b) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 697. (c) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605.

8. Nicolaou, K. C.; Finlay, M. R. V.; Ninkovic, S.; Sarabia, F. *Tetrahedron* **1998**, *54*, 7127.

9. Andrus, M. B.; Li, W.; Keyes, R. F. *Tetrahedron Lett.* **1998**, *39*, 5465.

10. Foster, M. P.; Concepción, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671.

11. Abe, H.; Kushida, K.; Shiobara, Y.; Kodama, M. *Tetrahedron Lett.* **1988**, *29*, 1401.

12. Suzuki, Y.; Ojika, M.; Sakagami, Y.; Fudou, R.; Yamanaka, S. *Tetrahedron* **1998**, *54*, 11399.

13. The thiazolo[5,4-*h*]quinolin-6-one is part of the skeleton of the marine natural product *kuanoniamine A*. Besson, T.; Rees, C. W.; Roe, D. G.; Thiéry, V. *J. Chem. Soc, Perkin Trans. 1* **2000**, 555.

14. Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487.

15. (a) Prakash, O.; Saini, N.; Sharma, P. K. *Synlett* **1994**, 221. (b) Moriarty, R. M.; Vaid, B. K.; Duncan, M. P.; Levy, S. G.; Prakash, O.; Goyal, S. *Synthesis* **1992**, 845.

16. Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394.

17. Cherest, M.; Lusinchi, X. *Tetrahedron Lett.* **1989**, *30*, 715.

18. For *General Procedures*, see reference 3.