HETEROCYCLES, Vol. 64, 2004, pp. 33 - 39
Received, 29th June, 2004, Accepted, 16th July, 2004, Published online, 17th July, 2004

ACCESS TO THE NEW ISOINDOLO[1,3]BENZOTHIAZOCINONES VIA THE COMBINATION OF *N*-ACYLIMINIUM CHEMISTRY AND FRIEDEL-CRAFTS TYPE π-CYCLIZATION

Armelle Cul,[a] Adam Daïch,[a]* Bernard Decroix,[a] Gérard Sanz,[b] and Luc Van Hijfte[b]

[a]Laboratory of chemistry, URCOM, EA 3221, UFR of Sciences & Techniques, University of Le Havre, B.P: 540, 25 rue Philippe Lebon, F-76058 Le Havre Cedex, France. [b]Johnson & Johnson, Pharmaceutical Research & Development, Division of Janssen-Cilag, Campus de Maigremont, B.P: 615, F-27106 Val-de-Reuil Cedex, France. adam.daich@univ-lehavre.fr

Abstract – New racemic and chiral [4,2]- and [3,5]benzothiazocines (**4**) and (**5**) in the isoindolinone series were synthesized easily in few steps based on the combination of *N*-acyliminium chemistry and π-cationic cyclization of acylium ions. The chemoselectivity observed during these processes, particularly in the reduction, the thioalkylation and the cyclization stages, were also discussed.

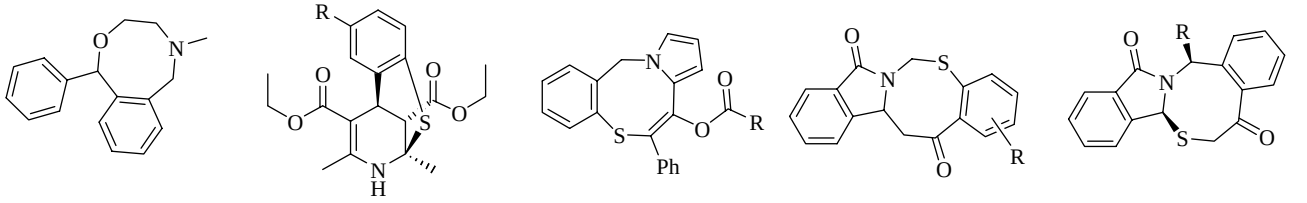
INTRODUCTION†

Benzene-fused eight-membered ring *N*,*O*-, and *N*,*S*-heterocycles have provided a rich source of central nervous system (CNS) and cardiovascular therapeutic agents. Compounds such as nefopam (**1**) (an analgesic 1*H*-[1,4]benzoxazocine),[1] substituted methano[1,3]benzothiazocine (**2**) (a calcium channel agonists),[2] and pyrrolo[1,5]benzothiazocine (**3**) (a molecular probe of the "peripheral-type" benzodiazepine receptors (PBR)),[3] are representative of such agents with interesting biological activity.

Because of the fact that [1,3]benzothiazocines are little explored, and as a continuation of our current research programs, we planned to access isoindolinone fused benzothiazocinones, such as the structures (**4**) and (**5**). The use of *N*-acyliminium chemistry in combination with Friedel-Crafts cyclization seemed to be a valuable strategy to provide these targets in an efficient and concise manner.

† This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday

Chart 1. Representative polycyclic benzothia(and oxa)zocine structures and the *N*,*S*-acetal targets.



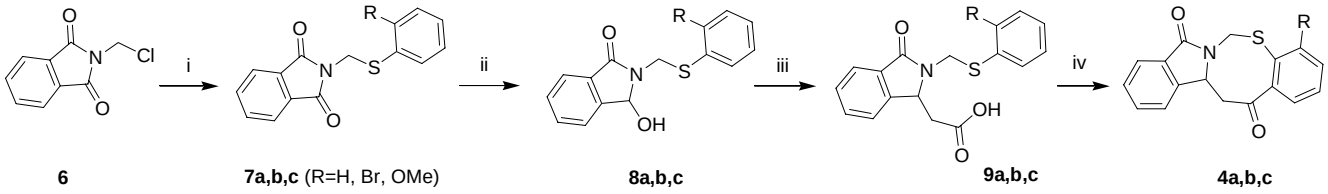
Nefopam (**1**) | Methanobenzothiazocines (**2**) R=H, NO_2 | Pyrrolobenzothiazocines (**3**) R=Me, NMe_2 | [4,2]Benzothiazocines (**4**) R=H, Br, OMe | [3,5]Benzothiazocines (**5**) R=H, Me

Because of the fact that [1,3]benzothiazocines are little explored, and as a continuation of our current research programs, we planned to access isoindolinone fused benzothiazocinones, such as the structures (**4**) and (**5**). The use of *N*-acyliminium chemistry in combination with Friedel-Crafts cyclization seemed to be a valuable strategy to provide these targets in an efficient and concise manner.

RESULTS AND DISCUSSION

As depicted in Scheme 1, our strategy relied on the synthesis of acetic acid intermediate (**9**) as a π-cationic cyclization precursor. This latter should be accessible from the halide (**6**) in a three step-sequence.

Scheme 1. Synthetic sequence leading to isoindolo[1,3]benzothiazocines (**4a-c**).



6 | **7a,b,c** (R=H, Br, OMe) | **8a,b,c** | **9a,b,c** | **4a,b,c**

Key: (i) Aryl mercaptan, MeONa, DMF, rt, 12 h (87 to 91 %); (ii) 1°- $NaBH_4$, MeOH, 0 °C to rt, 2°- 10% HCl (97 to 98 %); (iii) 1°- $Ph_3P{=}CHCO_2Et$, toluene, reflux, 2 h, 2°- K_2CO_3, MeOH, H_2O, 60 °C, 2 h (57 to 87 %); (iv) 1°- $SOCl_2$, DCM, reflux, 1 h, 2°- $AlCl_3$ (99.99 %), DCM, 0 °C to rt, 1 h (35 to 78 %).

In fact, the commercially available 1-chloromethylphthalimide (**6**) was alkylated with slight excess of *ortho*-substituted thiophenol (**7a-c**) in alkaline medium (87 to 91%). Regioselective reduction of the resulted imides (**7a-c**) was performed with a large excess of $NaBH_4$ (4 to 6 equiv.) in analogy to our earlier reports, and afforded (**8a-c**) in excellent yields (97-98%, see Table 1).[4b] In some cases, to avoid the poor solubility of the imide (**7**), allied to the laborious work-up encountered during these processes, a small quantity of THF as co-solvent was added. The next step consisted of the conversion of hydroxy lactams (**8a-c**) to the acetic acid derivatives (**9a-c**) by applying the tandem Wittig type condensation/alkaline hydrolysis in one-pot procedure, followed with an acidic treatment.[5] Finally, the acid (**9**) was treated with 1.2 equiv. of thionyl chloride in dichloromethane at reflux for 1 h and the resulting acid chloride under Friedel-Crafts cyclization conditions using aluminum trichloride (99.99% purity) as catalyst gave the expected tetracyclic ketone (**4**) in moderate (35%) to good (78%) yields (see Table 1). The modest yield

obtained in the case of the methoxy-substituted derivative (**4c**) could be explained by the cleavage of the thioether linkage in acidic medium.

Table 1. Yields of intermediates (**7-9a,b,c**) and corresponding isoindolo[1,3]benzothiazocines (**4a,b,c**).

Product[a]	R Group	Imide (**7**) Yield (%)	Hydroxy lactam (**8**) Yield (%)	Acid (**9**) Yield (%)	Tetracyclic Ketone (**4**) Yield (%)
a	H	91	97	60	78
b	Br	87	98	87	71
c	OMe	90	97	57	35[b]

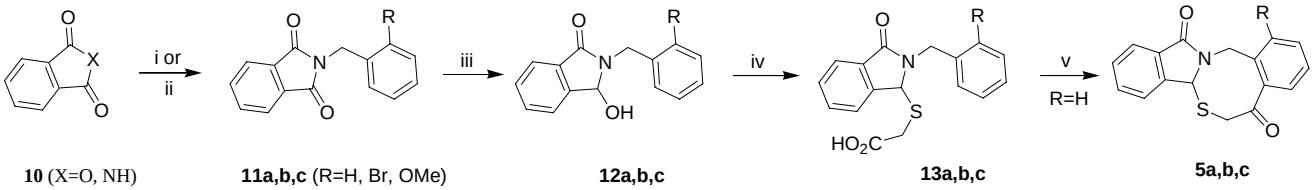
[a]Yields indicated were obtained after recrystallization for imides (**7**), hydroxy lactams (**8**) and acids (**9**) and after chromatography purification of cyclic *N,S*-acetals (**4**). [b]An important decomposition of the acid (**9**) as starting material was observed.

Having established that the combination of *N*-acyliminium species/π-cyclization route is effective for the preparation of the isoindolo[1,3]benzothiazocine derivatives (**4a-c**), we decided to elaborate another class of acylium precursors in which a sulfur atom is attached to the angular carbon of the isoindolinone nucleus. As depicted in Scheme 2, the prerequisite acetic acid derivatives (**13a-c**) were obtained in a three-step sequence. The hydroxy lactams (**12a-c**) were obtained in good yields from phthalimide (**10**, X=NH) by *N*-alkylation (87 to 91%) followed by the sodium borohydride reduction of the intermediate known imides (**11a-c**) (97 to 98%).[7] Since it has been demonstrated that hydroxy lactams with various sulfur nucleophiles underwent an acid-catalyzed substitution reaction involving *N*-acyliminium species,[6] we attempted to synthesize acid derivatives (**13a-c**). In fact, treatment of **12a-c** with thioglycolic acid (1.5 equiv.) and a catalytic amount of *p*-toluenesulfonic acid at room temperature for 24 h afforded the expected acids (**13a-c**) in very good yields (89 to 95%). The separation of the acid **13** from the unreacted thioglycolic acid was accomplished easily by treatment of the reaction mixture with potassium carbonate solution at 40 °C for 1 h followed by dichloromethane extraction, and finally acidification with aqueous hydrochloric acid (10%) at 0 °C.

The above acid derivative (**13a**), chosen as a model substrate, was treated with thionyl chloride under reflux of dichloromethane for 2 h and the resulting acid chloride in the presence of 3 equiv. of aluminum trichloride (99.99% purity) gave the expected tricyclic thiazocinone (**5a**) in good yield (87%). Under similar conditions, the thioglycolic acid derivatives (**13b,c**) seemed to be more fragile than **13a** under acidic conditions. In both cases, the sole product obtained from the reaction mixture was the starting hydroxy lactams congeners (**12b,c**) which resulted from the departure of the sulfur fragment under acidic conditions followed by the hydration of the *N*-acyliminium intermediates during the work up hydrolysis.[8] This result could be explained by the deactivation of the aromatic ring system by the bromide or the methoxy group at the *ortho* position of the benzene ring. In these cases only the cleavage of the thioether linkage, which

constitutes a competing process to the detriment of the π-cyclization, takes place. All attempts to optimize the reaction by different experimental conditions did not give satisfaction.

Scheme 2. Access to the positional isomers (**5a-c**) of isoindolo[1,3]benzothiazocines (**4a-c**).



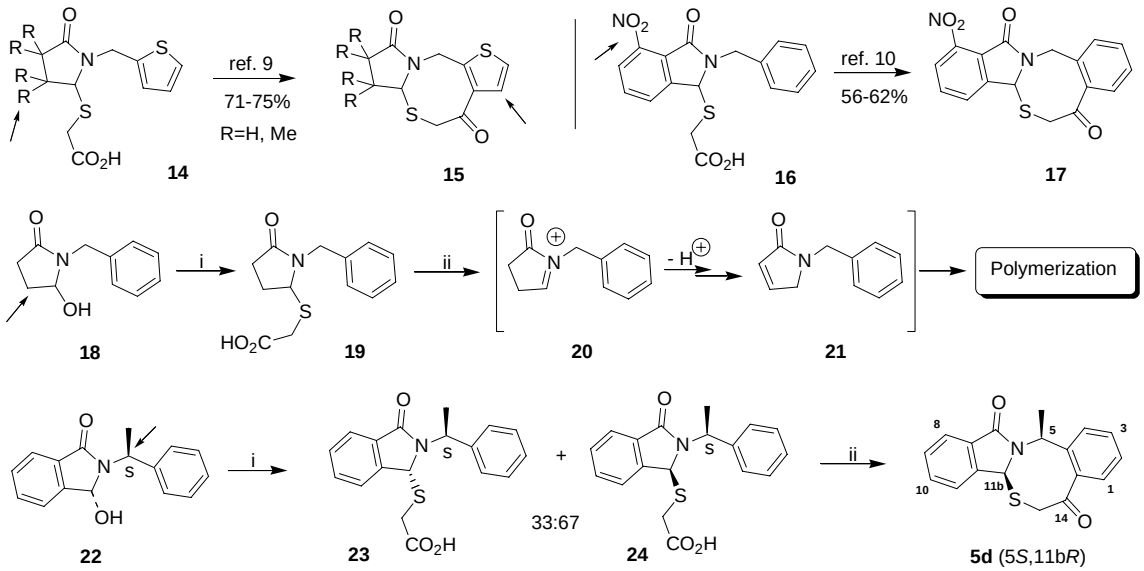
10 (X=O, NH) **11a,b,c** (R=H, Br, OMe) **12a,b,c** **13a,b,c** **5a,b,c**

Key: (i) From anhydride (**10:** X=O): amine, toluene, NEt_3, reflux, DS (see ref. 7); (ii) From imide (**10:** X=NH): Halide, KI, K_2CO_3, 18-C-6, toluene, reflux, 12 h (78 to 91 %); (iii) 1°- $NaBH_4$, MeOH, 0 to 10°C, 2°- 10% HCl (97 to 98 %); (iv) 1°- $HSCH_2CO_2H$, PTSA, DCM, rt, 24 h, 2°- K_2CO_3, H_2O, 40 °C, 1 h, 3°- 10% HCl (89 to 95 %); (iv) 1°- $SOCl_2$, DCM, reflux, 2 h, 2°-$AlCl_3$ (99.99 %), DCM, 0 °C to rt, 2 h (87 % for **5a**).

Compound (**5**) and all other unknown intermediates reported herein (**4**, **7-9**, and **12-13**) were identified by spectroscopic methods including ^{1}H-NMR, ^{13}C-NMR, DEPT program, IR, coupling GC-MS spectra as well as by microanalysis.

Based on our precedent work, in which the pyrrolo(or tetramethylpyrrolo)[1,3]benzothiazocinones (**15**) (71-75%)[9] and isoindolo[1,3]benzothiazocinones (**17**) (56-62%)[10] were isolated in appreciable yields (Scheme 3), we planned to extend this synthetic approach to other systems. So, the elaboration of novel *N*,*S*-heterocyclic systems as pyrrolidone and isoindolinone was explored.

Scheme 3. Generalization of the sequence to a succinamidal (**18)** and a chiral isoindolone (**22**) series



14 **15** **16** **17**

18 **19** **20** **21**

22 **23** **24** **5d** (5*S*,11b*R*)

Conditions and reagents: (i) 1°- $HSCH_2CO_2H$, PTSA, DCM, rt, 12 h, then 2°- K_2CO_3, MeOH, H_2O, 60 °C, 1 h (89 % for **19** and 88 % for **23/24** as a 33:67 mixture); (ii) 1°- $SOCl_2$, DCM, reflux, 1 h, then 2°-$AlCl_3$ (99.99 %), DCM, 0 °C, 1 to 2 h (68 % for **5d**).

As highlighted in Scheme 3 and according to our sequential set of reactions, the *N*-benzylsuccinamidal (**18**)[11] was transformed into the corresponding thioglycolic acid (**19**) in good yield (89 %). This acid

derivative, upon treatment under our standard cyclization conditions, furnished, whatever the changes operated in the experimental conditions, a polymeric material. This behavior of **19**, could be explained easily by the fact that the α-alkylsulfanyl lactam such as **19** could generate a *N*-acyliminium cation (**20**) in acidic medium.[8] This latter, upon acid catalyzed olefin isomerization,[12] could provide the instable enamide (**21**) which polymerized rapidly.[13]

Our next concern was the evaluation of the impact of the chirality in this process. The α-hydroxy lactam (**22**) was obtained in 92 % yield in a 5.5/4.5 mixture of two diastereomers from the corresponding enantiopure (*S*)-imide by the tandem sodium borohydride/methanol/hydrochloric acid reduction protocol.[5] Subjection of **22** to thioglycolic acid in dichloromethane with *p*-toluenesulfonic acid as catalyst led to a 33:67 mixture of two thioglycolic acids as diastereomeric pairs (**23**) and (**24**) (88 %). An enriched 15:85 mixture of **23**:**24** was obtained by a recrystallization from dry ethanol and no enantiopure **23** and/or **24** was isolated whatever the use of other solvent in this process. This mixture was then treated with thionyl chloride (1.2 equiv. in dichloromethane at reflux for 1 h) followed by aluminum trichloride (3 equiv. in dichloromethane at 0 °C for 1 to 2 h) to give the cyclic product (**5d**) in an equivalent diastereomeric ratio (15:85) in 68 % yield. The elucidation of the absolute configuration of the major tricyclic ketone, which was obtained in pure form by twice fractional crystallization from dry ethanol (all attepts of separation by chromatography failed), was based on our prior experience in the field.[5] The *cis*-relation-ship between H_5 and the newly created stereocenter H_{11b} was proved by NOE measurements. In this respect, the irradiation of H_{11b} (s, δ =5.75 ppm) shows significant NOE effect for the proton H_5 (q, δ=5.79 ppm). These results demonstrate clearly that the isoindolobenzothiazocinone (**5d**) have a (5*S*,11b*R*) configuration ($[\alpha]_D$=+124.5° (c 0.2 *M*, ethanol)).[14]

CONCLUSION

The synthetic sequence reported in this paper constitutes an excellent, short, and general protocol to access various isoindolo[1,3]benzothiazocinones of type (**4**) and their positional [5,3]-isomers of type (**5**). These polyheterocyclic systems were obtained in appreciable overall yields and could be obtained in a large scale. Consequently, these *N*,*S*-acetals might find application as building blocks in synthesis of potentially bioactive compounds and could constitute also excellent precursors for new synthetic investigations.

ACKNOWLEDGEMENTS

We acknowledge the Johnson & Johnson, Pharmaceutical Research & Development, Division of Janssen-Cilag, for scientific and financial support of this program. We thank also the Region of “Haute Normandy” in France for a “Regional-Industrial Graduate Fellowship” (BRI), **1998-2001**, attributed to Armelle Cul.

REFERENCES AND NOTES

1. M. W. Klohs, M. D. Draper, F. J. Petracek, K. H. Ginzel, and O. N. Ré, *Arzneim. Forsch.*, 1972, **22**, 132.
2. J. J. Baldwin, D. A. Claremon, P. K. Lumma, D. E. McClure, S. A. Rosenthal, R. J. Winquist, E. P. Faison, G. J. Kaczorowski, M. J. Trumble, and G. M. Smith, *J. Med. Chem.*, 1987, **30**, 690.
3. G. Campiani, V. Nacci, I. Fiorini, M. P. De-Filippis, A. Garofalo, S. M. Ciani, G. Greco, E. Novellino, C. Manzoni, and T. Mennini, *Eur. J. Med. Chem.*, 1997, **32**, 241.
4. (a) N. Hucher, A. Daïch, and B. Decroix, *Org. Lett.*, 2000, **2**, 1201. (b) N. Hucher, B. Decroix, and A. Daïch, *J. Org. Chem.*, 2001, **66**, 4695.
5. A. Chihab-Eddine, A. Daïch, A. Jilale, and B. Decroix, *Heterocycles*, 2002, **58**, 449.
6. For this subject, see: (a) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron*, 2000, **56**, 3817. (b) B. E. Maryanoff, H. C. Zhang, J. H. Cohen, I. J. Turchi, and C. A. Maryanoff, *Chem. Rev.*, 2004, **104**, 1431.
7. For the synthesis of imides (**12a-c**), see respectively: (a) K. Sasaki, Y. Shibata, Y. Hashimoto, and S. Iwasaki, *Biol. Pharm. Bull.*, 1995, **18**, 1228. (b) T. G. M. Dahr, Z. Shen, H. H. Gu, P. Chen, D. Norris, S. H. Watterson, S. K. Ballentine, C. A. Fleener, K. A. Rouleau, J. C. Barrish, R. Townsend D. L. Hollenbaugh, and E. J. Iwanowicz, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3557. (c) Y. Kato, M. Takemoto, and K. Achiwa, *Chem. Pharm. Bull.*, 1999, **47**, 529.
8. Few reports concerning the generation of *N*-acyliminiums species, from corresponding α–alkylsulfanyl- and α–arylsulfanyl lactams have been mentioned in the literature. For representative examples see: (a) ref. 4 (b) and references cited therein. (b) A. Padwa and A. G. Waterson, *J. Org. Chem.*, 2000, **65**, 135. (c) A. Padwa and A. G. Waterson, *Tetrahedron*, 2000, **56**, 10159 and references cited therein.
9. A. Mamouni, A. Daïch, and B. Decroix, *Synth. Commun.*, 1997, **27**, 2249.
10. A. Chihab-Eddine, A. Daïch, A. Jilale, and B. Decroix, *J. Heterocycl. Chem.*, 2000, **37**, 1543.
11. A. Guzman, M. Romero, and J. M. Muchowski, *Can. J. Chem.*, 1990, **68**, 791.
12. A. Chihab-Eddine, A. Daïch, A. Jilale, and B. Decroix, *Tetrahedron Lett.*, 2001, **42**, 573.
13. For similar profile in the oxygen series, see our previously reports in the following reference: A. Mamouni, Š. Marchalín, A. Daïch, and B. Decroix, *Heterocycles*, 2001, **54**, 275.
14. General protocol for the π-cationic cyclization of acetic acid and thioglycolic acid derivatives: Representative procedure for the synthesis of (5*S*,11b*R*)-5,11*b*-dihydro-5-methylisoindolo[1,2-*d*][3,5]-benzothiazocine-7,14(13*H*)-dione (**5d**). To a stirred solution of acids derivatives (**23**:**24**) (1.3 g, 3.97 mmol) in dry dichloromethane (50 mL) under argon atmosphere was added slowly 1.2 equivalents of freshly distilled thionyl chloride (0.57 g, 4.76 mmol) and the mixture was allowed to react at reflux for 1 h. After cooling and concentration under *vacuo*, the residue was dissolved in dry dichloromethane

(50 mL). The mixture was cooled at 0 °C and treated with 3 equivalents of aluminium trichloride (99.99%) (1.58 g, 11.9 mmol) over a period of 5 min under vigorous stirring. After 1 to 2 h of reaction at this temperature, the solution was poured onto a mixture of cold water and crushed ice and separated. The aqueous solution was extracted again twice with dichloromethane and the organic layers were washed with water, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was isolated as a white solid in 68% yield and after twice recrystallization from dry ethanol give pure **5d**, mp=102 °C (decompo); $[\alpha]_D$=+124.5° (c 0.2 *M*, ethanol); IR (KBr) ν 3082, 2968, 1708, 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.88 (d, 3H, CH_3, *J*=8.0 Hz), 2.78 (d, 1H, CO-CH_2, *J*=15.8 Hz), 2.96 (d, 1H, CO-CH_2, *J*=15.8 Hz), 5.75 (s, 1H, S-CH), 5.79 (q, 1H, CH, *J*=8.0 Hz), 6.91-7.42 (m, 4H, $4H_{aromatic}$), 7.56-7.75 (m, 3H, $3H_{aromatic}$), 7.84 (d, 1H, $1H_{aromatic}$, *J*=8.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 18.1 (CH_3), 36.1 (CH_2), 46.2 (CH), 59.0 (CH), 120.9 (CH), 122.1 (CH), 123.2 (CH), 124.9 (CH), 126.1 (2xCH), 129.0 (CH), 131.0 (Cq), 133.1 (CH), 135.0 (Cq), 135.2 (Cq), 141.4 (Cq), 163.4 (CO), 205.2 (CO); MS EI, 70 ev) *m/z*: 309 (M^+); *Anal.* Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.51; H, 4.73; N, 4.35.