Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7817–7820

Synthesis of regiospecifically polysubstituted pyridazinones

João X. de Araújo-Júnior,[a,c] Martine Schmitt,[a,*] Cyril Antheaume[a,b] and Jean-Jacques Bourguignon[a]

[a]*Institut Gilbert Laustriat, UMR 7175, 74 route du Rhin, BP 60024, 67401 Illkirch, France*
[b]*Service Commun de RMN, Faculté de Pharmacie, 74 route du Rhin, BP 60024, 67401 Illkirch, France*
[c]*Escola de Enfermagem e Farmacia, Instituto de Química e Biotecnologia, Universidade Federal de Alagoas, cidade Universitaria, 57.072-970 Maceió-AL, Brazil*

Received 11 June 2007; revised 3 August 2007; accepted 4 September 2007
Available online 6 September 2007

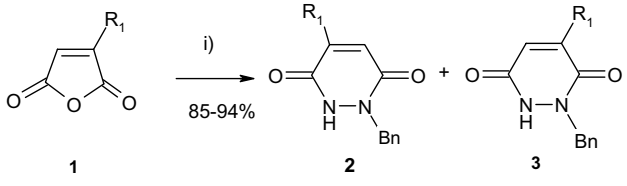
Abstract—Desymmetrization of pyridazine-3,6-diones by the use of *N*-benzyl protective groups leads to useful starting materials for building polysubstituted pyridazine libraries in a regioselective manner.

Pyridazine derivatives, in particular pyridazinones, present various pharmacological properties.[1–7] In most cases, the compounds bear an aryl group in position 6. Some of them are also substituted in position 4[2] or 5.[1,3b] They are prepared by means of classical methodologies,[1,3,4] generally offering fair structural diversity. More recent approaches involving palladium cross-coupling reactions were developed starting from 3,6-dichloropyridazines,[8–12] 4-bromopyridazines,[13–16] or *O*-tosyl pyridazines.[17,18] However, they still presented limited structural variations.

To control the regioselectivity of the substitution, we report an original method using desymmetrization of pyridazine-3,6-diones by a *N*-benzyl group. These dissymmetric intermediates permit regioselective control of chemical variations on different positions 3, 4, 5 and 6 of the pyridazine backbone.

Thus, the treatment of substituted maleic anhydrides **1** with *N*-benzyl hydrazine in acidic medium (Scheme 1) gave a mixture of the expected *N*-benzyl pyridazine 3,6-diones **2** and **3**.

Due to their close R_f values, the regioisomers could not be separated by column chromatography. However, a simple trituration of the crude material containing **2c** and **3c** (R_1=Br) with a mixture of ethyl acetate and ethyl ether (1/4) gave an insoluble residue, which was recovered and recrystallized from ethanol, giving a pure regioisomer **2c**.



Entry	R_1	Total yield (%)	2%[b](%)[c]	3%[b](%)[c]
a	Me	85	50 (45)	50 (40)
b	Ph	90	68 (62)	32 (28)
c	Br	94	55 (53)	45 (41)

a) total recovery of 2 and 3 after purification by recrystallization, b) 2/3 ratio characterized by ^{1}HNMR in the reaction mixture, c) recovery after recrystallisation

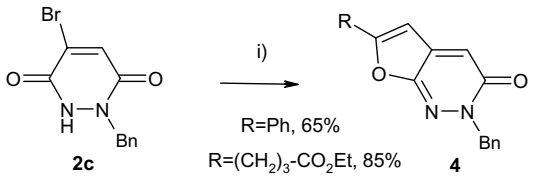
Scheme 1. Preparation of substituted *N*-benzyl-pyridazine-diones **2** and **3** as pure regioisomers. Reagents and conditions: (i) $BnNHNH_2$, HCl, H_2O, reflux, 12 h.

The structure of isomer **2c** was established as the Sonogashira-type reaction product using phenylacetylene or aliphatic acetylene spontaneously cyclized yielding furo-pyridazones **4** (Scheme 2).[17,20]

The filtrate was recrystallized from isopropyl ether affording the other isomer **3c**. Similar treatments could

Keywords: *N*-Benzyl 4 (5)-substituted pyridazine 3,6-diones amination; Palladium cross coupling reaction; Microwave heating; Suzuki; Sonogashira.
* Corresponding author. Tel.: +33 390 244231; fax: +33 390 244310; e-mail: schmitt@pharma.u-strasbg.fr

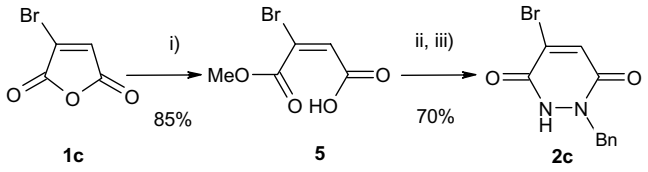
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.09.013



Scheme 2. Formation of furopyridazinones **4**. Reagents and conditions: (i) R-≡, CuI, $PdCl_2(PPh_3)_2$ (3.5 mol%), NEt_3, μ-waves, 80 °C, 5 min.

be efficiently applied to other mixtures of regioisomers (**2a**/**3a** and **2b**/**3b**). When applying such simple treatments on larger scales, several grams of each pure regioisomer could be prepared and submitted to further reactions.

Regioisomer **2c** could also be selectively prepared starting from bromo-maleic anhydride **1c**, as shown in Scheme 3. The first methanolysis of anhydride in acid medium led to monoacid **5**, as reported in the recent literature.[19] Coupling this mono acid **5** with *N*-benzylhydrazine yielded hydrazide as an intermediate, which easily cyclized to afford the pure regioisomer **2c** bearing the bromine atom in position 4.

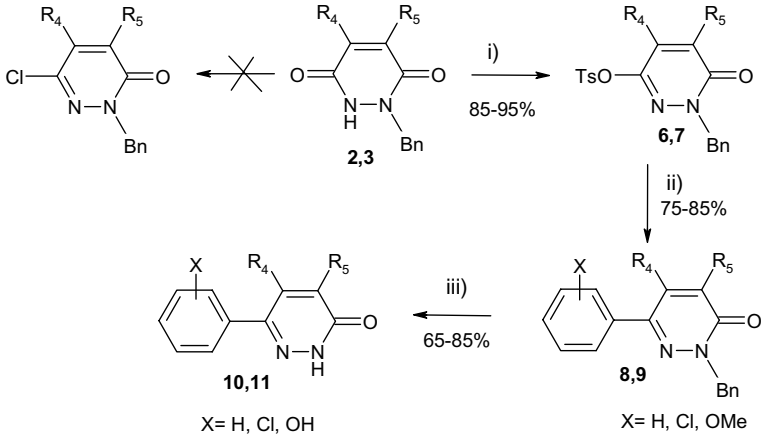


Scheme 3. Non-ambiguous preparation of **2c** as a single regioisomer. Reagents and conditions: (i) MeOH, rt; (ii) $ClCO_2iBu$, DCM, −25 °C to rt; (iii) $BnNHNH_2$, HCl, TEA, DCM, −25 °C to rt.

Pyridazine-3,6-diones **2** and **3** are suitable intermediates for the preparation of 6-aryl-pyridazinones by means of Suzuki-type reactions (Scheme 4).[20] However, the classical activation step using $POCl_3$ at 80 °C gave a complex reaction mixture, probably as a result of partial removal of the benzyl group. Thus the *O*-tosyl derivatives (**6** and **7**) were prepared in nearly quantitative yield, and reacted in the presence of different aryl boronic acids and $Pd(PPh_3)_4$ to yield the corresponding pyridazinones **8** and **9** in satisfactory yields.[20] Deprotection of the benzyl group was performed using $AlCl_3$ as Lewis catalyst and under microwave conditions (5 min) leading to the free pyridazine-3-ones **10** and **11**. The yields were satisfactory. However, as a limitation for generalization of the method, a quantitative *O*-demethylation was also observed, when the aromatics were bearing methoxy groups.

The 4 (or 5)-bromo-1-*N*-benzyl pyridazine-3,6-diones (**2c** and **3c**) are more interesting key intermediates, as the halide constitutes an additional anchor to introduce diversity, mainly through Pd(0) coupling reactions (Schemes 5 and 6).

The bromo compound **2c** could be first reacted in Suzuki-type reactions yielding intermediates **2b** (Ar_1 = Ph) or **12** ($Ar_1 \neq$ Ph), which could be further reacted in differ-

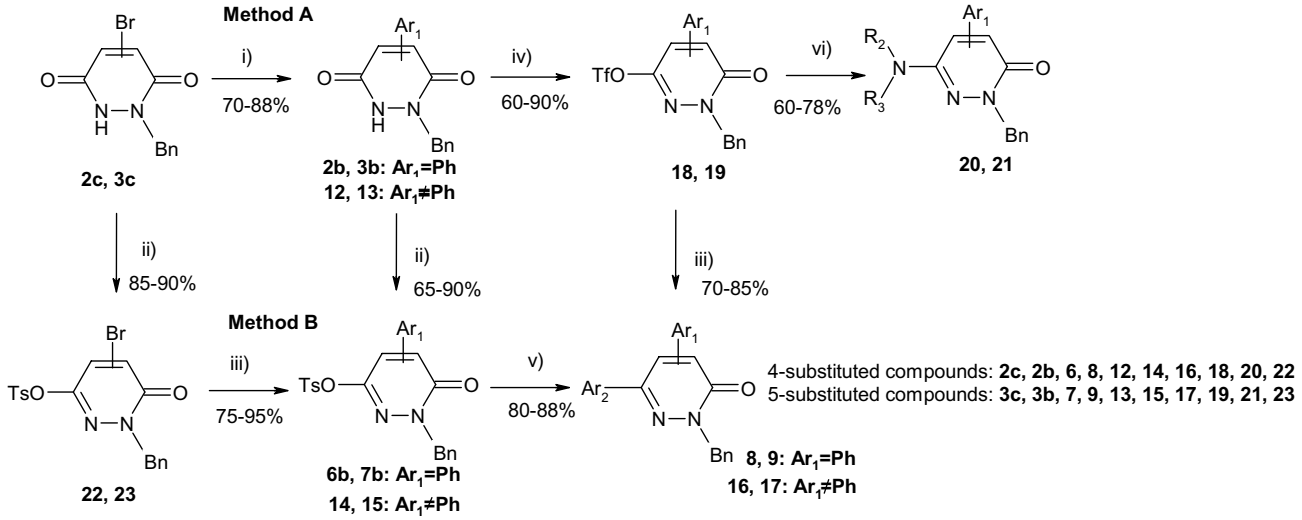


2,6,8,10: R_4=Me, Ph, R_5=H
3,7,9,11: R_4=H, R_5= Me, Ph

Starting material	**6,7** yield(%)	X	**8,9** yield(%)	**10,11** yield(%)
2a	**6a**(88)	H	**8a**(75)	**10a**(85)
		4-Cl	**8b**(80)	**10b**(73)
		4-OMe	**8c**(85)	**10c**(65)[a]
3a	**7a**(85)	H	**9a**(78)	**11a**(79)
		4-OMe	**9b**(82)	
2b	**6b**(90)	4-OMe	**8d**(70)	
3b	**7b**(95)	4-OMe	**9d**(82)	

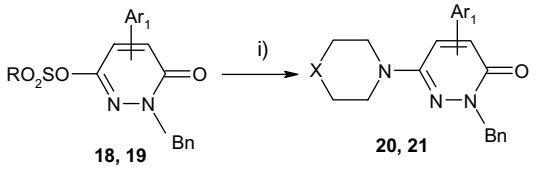
[a] OMe→OH

Scheme 4. Access to 4 (or 5) substituted 6-aryl-pyridazinones. Reagents and conditions: (i) TsCl, pyridine, rt; (ii) $ArB(OH)_2$, $Pd(PPh_3)_4$ (7%), μw, DME, 30 min, 110 °C; (iii) $AlCl_3$ (2 equiv), μw, toluene, 5 min, 140 °C.



Starting material	Method	Ar_1	Cpd Yield(%)	Cpd Yield(%)	Ar_2	Cpd Yield(%)
2c	A	Ph	**2b** (70)	**18a** (85)	4-OMe Ph	**8d** (81)
18a	-	-	**-**	**-**	3-OMe-Ph	**8e** (79)
2c	A	4-OMe Ph	**12a** (70)	**18b** (90)	Ph	**16a** (75)
12a	-	-	**-**	**14a** (78)	Ph	**16a** (80)
3c	A	Ph	**3b** (92)	**19a** (65)	4-OMe Ph	**9d** (84)
19a	-	-	**-**	**-**	3,4-OMePh	**9e** (81)
3c	A	4-OMe Ph	**13a** (60)	**19b** (88)	Ph	**17a** (82)
3c	A	3-OMe-Ph	**13b** (75)	**19c** (90)	-	**-**
22	B	Ph	**6b** (90)	**-**	4-OMe Ph	**8d** (70)
23	B	Ph	**7b** (75)	**-**	4-OMe Ph	**9d** (80)
23	B	4-OMe Ph	**15a** (68)	**-**	Ph	**17a** (88)

Scheme 5. Introduction of chemical diversity on the pyridazine ring by Suzuki/amination reactions. Reagents and conditions: (i) $R_1B(OH)_2$, $Pd(PPh_3)_4$ (7%), μw, DME, 20 min, 160 °C; (ii) TsCl, pyridine; (iii) $ArB(OH)_2$, $Pd(PPh_3)_4$ (7%), μw, DME, 20 min, 100 °C; (iv) Tf_2O, pyridine, 0 °C; (v) $Ar_2B(OH)_2$, $Pd(PPh_3)_4$ (7%), μw, DME, 30 min, 110 °C; (vi) see Scheme 6.



Starting material	R	X	n	Time (min)	**20, 21** (%)
7b	4-MePh	O	5	60*	**21a**(traces)
19a	CF_3	O	3	15	**21a**(30)
19a	CF_3	O	5	40	**21a**(78)
19a	CF_3	N-Ph	4	40	**21b**(68)
19c	CF_3	N-Ph	4	40	**21c** (62)
18a	CF_3	O	5	40	**20a**(60)
18b	CF_3	O	5	40	**20b**(65)

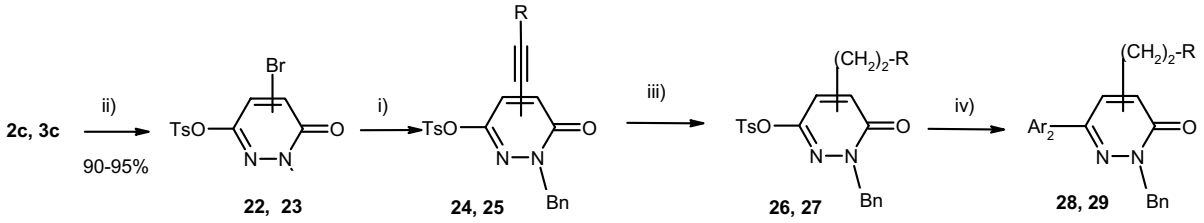
* at 200°C; n: number of equiv. of amine

Scheme 6. Preparation of amino-pyridazinones. Reagents and conditions: (i) μw, 180 °C, 12 bar, 70–95% yield.

ent ways (Scheme 5). The corresponding OTs derivatives **6** or **14** could be submitted to a second palladium cross-coupling reaction (PCCR). In particular, the Suzuki-type reaction using various aryl boronic acids allowed introduction in a very straightforward manner of various substituted aryl groups in position 6 (compounds **8** and **16**, respectively). However, the OTs derivative was not reactive toward amination reactions. The replacement of the OTs by an OTf group (derivatives **18**) dramatically increased the reactivity in particular towards amination reactions, (Scheme 6), and afforded the corresponding amino-compounds **20** in good yields (5 equiv of amine, 40 min, μw, 180 °C, 12 bar, 70–95% yield).[20,21]

Similar results were obtained with the other regioisomer **3c**. Finally, the difunctionalized pyridazinones **22** and **23** could be prepared, and presented the same order of reactivity toward PCCR (4-Br > 6-OTs, Schemes 5 and 7). The sequence combining Suzuki (**3c**→**13**)/activation (**13**→**19**)/Suzuki (**19**→**17**) reactions could be compared with an alternative pathway combining activation (**3c**→**23**) and two successive Suzuki-type reactions (**23**→**15**→**17**, Scheme 5).

Finally, the most efficient pathway will be selected depending on the nature of the involved reactions (nature of activating group or type of PCCR). As an example of the importance of the pathway selection compound **28** could be prepared from **2c** following a sequence involving the activation of the unprotected amide leading to tosylate **22**, which was reacted in a Sonogashira-type reaction giving the acetylenic derivative **24.** Hydrogenation of the alkyne led to the saturated side chain (compound **26**). Finally, a Suzuki-type reaction permitted to substitute



4-substituted compounds: **2c, 22, 24, 26, 28**
5-substituted compounds: **3c, 23, 25, 27, 29**

	R	Yields % 24	25	26	27	28	29
a	$(CH_2)_3NHBOC$	91	72	90	82	91	85
b	$(CH_2)_3OBn$ *	89	95	88	88	70	71
c	$(CH_2)_3CO_2Et$	79	77	99	82	67	85

* after hydrogenation OBn→OH

Scheme 7. Introduction of chemical diversity on the pyridazine ring by means of Sonogashira/Suzuki sequential reactions. Reagents and conditions: (i) CuI, TEA, CH_3CN, $PdCl_2(PPh_3)_2$, (3.5%), Ph-≡, μw, 5 min, 80 °C; (ii) TsCL, pyridine; (iii) H_2, Pd/C, MeOH; (iv) $Ar_2B(OH)_2$, $Pd(PPh_3)_4$ (7%), μw, 30 min, 120 °C.

the tosylate giving the expected pyridazinone **28** (Scheme 7),[20] whereas direct Sonogashira-type reaction in the vicinity of a free NH-amide group gave quantitatively the furo-pyridazinone **4** (Scheme 2).

After removal of the protective benzyl group as described above, the second amide function opened the ways to supplementary structural variations around the pyridazine backbone.

In conclusion the reported methodologies based on the desymmetrization of pyridazin-3,6-dione by means of *N*-benzyl-hydrazine and maleic anhydrides led to valuable intermediates possessing up to three different anchors able to introduce large diversity for the synthesis of regiospecifically poly substituted pyridazines.

Acknowledgement

Financial supports (Proc No. 0085057) of CAPES/Brazil to J.X.A.-J. and Cofecub are acknowledged. The authors thank Dr. Gilbert Schlewer for helpful discussions and encouragement.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.013.

References and notes

1. Wermuth, C. G.; Bourguignon, J. J.; Schlewer, G.; Gies, J. P.; Schoenfelder, A.; Melikian, A.; Bouchet, M. J.; Chantreux, D.; Molimard, J. C.; Heaulme, M.; Chambon, J. P.; Biziere, C. *J. Med. Chem.* **1987**, *30*, 239–249.
2. Velentza, A. V.; Wainwright, M. S.; Zasadzki, M.; Mirzoeva, S.; Schumacher, M.; Haiech, J.; Focia, P. J.; Egli, M.; Waterson, D. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3465–3470.
3. (a) Wermuth, C. G.; Bourguignon, J. J.; Hoffmann, R.; Boigegrain, R.; Brodin, R.; Kan, J. P.; Soubrié, P. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 833–838; (b) Contreras, J. M.; Parrot, I.; Sippl, W.; Rival, Y. M.; Wermuth, C. G. *J. Med. Chem.* **2001**, *44*, 2707–2718.
4. Contreras, J. M.; Rival, Y. M.; Chayer, S.; Bourguignon, J. J.; Wermuth, C. G. *J. Med. Chem.* **1999**, *42*, 730–741.
5. Schmitt, M.; Bourguignon, J. J.; Barlin, G. B.; Davies, L. P. *Aust. J. Chem.* **1997**, *50*, 779–785.
6. Albright, J. D.; Moran, D. B.; Wright, W. B.; Collins, J. B.; Beer, J. B.; Lippa, A. S.; Greenblatt, E. N. *J. Med. Chem.* **1981**, *78*, 592–600.
7. Rival, Y.; Hoffmann, R.; Didier, B.; Rybaltchenko, V.; Bourguignon, J. J.; Wermuth, C. G. *J. Med. Chem.* **1999**, *41*, 311–317.
8. Turck, A.; Ple, N.; Mojovic, L.; Queguiner, G. *Diazines VII. Bull. Soc. Chim. Fr.* **1993**, *130*, 488–492.
9. Ohsawa, A.; Abe, Y.; Igeta, H. *Chem. Pharm. Bull.* **1980**, *28*, 3488–3493.
10. Goodman, A. J.; Stanforth, S. P.; Tarbit, S. *Tetrahedron* **1999**, *55*, 15067–15070.
11. Chekmarev, D. S.; Stepanov, A. E.; Kasatkin, A. N. *Tetrahedron Lett.* **2005**, *46*, 1303–1305.
12. Schmitt, M.; de Araújo-Júnior, J. X.; Bourguignon, J. J. *Mol. Divers.* **2006**, *10*, 429–434.
13. Bourotte, M.; Pellegrini, N.; Schmitt, M.; Bourguignon, J. J. *Synlett* **2003**, 1482–1484.
14. Coelho, A.; Novoa, H.; Peeters, H.; Blaton, N.; Sotelo, E. *Tetrahedron* **2003**, *61*, 4785–4791.
15. Coelho, A.; Sotelo, E.; Ravina, E. *Tetrahedron* **2003**, *59*, 2477–2484.
16. Crespo, A.; Meyers, C.; Coelho, A.; Yánez, M.; fraiz, N.; Sotelo, E.; Maes, B. U. W.; Laguna, R.; Cano, E.; Lemière, G. L. F.; Ravina, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1080–1083.
17. de Araújo-Júnior, J. X.; Schmitt, M.; Benderitter, P.; Bourguignon, J. J. *Tetrahedron Lett.* **2006**, *47*, 6125–6128.
18. Bourguignon, J. J.; Oumouch, S.; Schmitt, M. *Curr. Org. React.* **2006**, *10*, 277–295.
19. Batchelor, M. J.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, *5*, 985–995.
20. Supporting information available: Experimental procedures and spectral data. This material is available free of charge.
21. Microwave irradiation has been performed using biotage Initiator EXP (http://www.biotage.com).