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Pyridazines. Part 25: Efficient and selective deprotection of pharmacologically useful 2-MOM-pyridazinones using Lewis acids†

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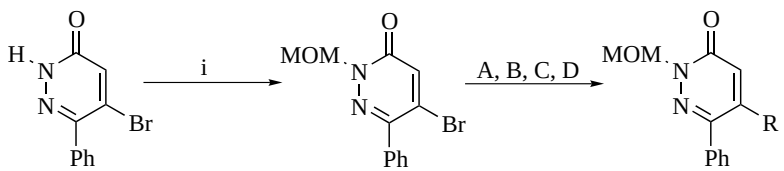
Abstract—An efficient and selective procedure for the cleavage of a methoxymethyl group at the 2-position in acid-sensitive pyridazinones is presented. Deprotection with Lewis acids (boron tribromide or aluminium chloride) affords 3(2*H*)-pyridazinones under mild conditions without affecting multiple bonds in substituents. © 2001 Elsevier Science Ltd. All rights reserved.

3(2*H*)-Pyridazinones have attracted considerable attention as a result of their pharmacological properties.[2] Several potentially useful drugs and pharmacological tools based on this pharmacophore have been developed in recent years, but there is ample scope for further exploration of this system. Several studies have indicated that the NH group adjacent to the carbonyl group in the azine system may be an essential structural requirement in the binding of 3(2*H*)-pyridazinones to a variety of biological receptors.[3] However, the numerous syntheses of 3(2*H*)-pyridazinones that have been published in recent years have made only limited progress in terms of the efficient protection of the 2-position in the heterocyclic ring. Although all structural studies on this nucleus have shown that 3(2*H*)-pyridazinones exist in the keto form,[4] reactions involving ambident rings that possess a tautomeric or mesomeric structure are often inefficient and lack regiocontrol.[4] For this reason several authors use pyridazinones as starting materials in which the 2-position is blocked. Most examples found in the literature concern analogues in which the 2-position is substituted by groups (such as $PhCH_2$, Me, Ph) that cannot be removed or are difficult to remove. Such groups do not represent protecting groups in the true sense and their use is limited to block the enolizable carbonyl group.

A survey of the literature on the removal of protecting groups[5] unfortunately revealed that, although there are excellent methods available for the deprotection of *O*-alkyl and *O*-alkyloxyalkyl groups, methods for the deprotection of the amide or lactam functionality are limited and usually require acidic conditions.[5] New protecting groups and/or reagents that are able to



1 **2** **3**

Scheme 1. (i): Cl-MOM, CH_2Cl_2, DMAP, *i*-Pr_2NEt, 0°C, 1 h. Method A: organotin, $PdCl_2(PPh_3)_2$, toluene, reflux. Method B: alkyne, CuI, $Pd(PPh_3)_2Cl_2$, DMF, 55°C. Method C: $ArB(OH)_2$, PPh_3, K_2CO_3, toluene/ethanol, reflux. Method D: alkene, $Pd(OAc)_2$, PPh_3, acetonitrile, reflux.

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† The previous paper in this series is: Efficient *N*-methylation of diversely substituted 3(2*H*)-pyridazinones using *N*,*N*-dimethylformamide dimethylacetal, see: Ref. 1.

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perform deprotection under mild and selective conditions are lacking and therefore new developments in this area are of great interest.

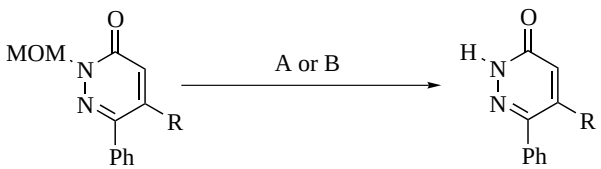
In connection with our search for novel pyridazinone-based antiplatelet agents,[6–8] and in order to test certain hypotheses suggested by molecular modelling studies concerning the structural requirements of a new family of platelet aggregation inhibitors, we decided to prepare a number of 3(2*H*)-pyridazinones including several with alkenyl or alkynyl groups at the 5-position (**5**).

The synthesis of these compounds by palladium-catalysed reactions involving readily obtainable 5-bromo-6-phenyl-3(2*H*)-pyridazinone (**1**)[9] would require protection of its NH group prior to submitting the substrate to the catalytic cycle.[10,11] Protection of **1** as its methoxymethyl (MOM) derivative **2** proceeded in 85% yield and subsequent reaction under Stille, Sonogashira, Suzuki or Heck conditions (Scheme 1, method A, B, C and D, respectively)[10,11] afforded good to excellent yields of compounds **3 a–h** after column chromatography (Table 1).

Once the coupling reactions had been successfully carried out, we proceeded to remove the protecting group under the acidic conditions typically used to hydrolyse MOM-derivatives.[12] This step involved treating the corresponding 5-substituted-3-pyridazinone **3** with excess 6N hydrochloric acid under reflux during 6–24 h. Treatment of **3b** and **3f** under these conditions afforded almost quantitative yields of **5b** (95%) and **5f** (98%), respectively, which have an acetyl group or aryl ring at 5-position. However, the use of these hard acid conditions for the removal of the MOM group proved to be unsuitable for the compounds containing alkenyl or alkynyl groups. The scope of this transformation is therefore limited since the highly acidic conditions required are not tolerated by sensitive functionalities and, indeed, most of the experiments undertaken led to complex product mixtures.

The failures discussed above can be attributed to the electrophilic addition of hydrochloric acid to the multiple bond, evidence of which was provided by the isolation of compounds **4a** (78%) and **4b** (84%) (Scheme 2) upon deprotection of **3i** and **3g**.[13] Is important to note that, according to the NMR data,[13] addition of HCl to the acetylene **3g** occurs in an anti-Markovnikov fashion. In order to solve these problems we attempted the cleavage of the methoxymethyl group from pyridazinones **3** by replacing 6N HCl with the milder Lewis acids, which have come to be regarded as reagents of choice for the efficient cleavage of ethers.[5]

We found that boron tribromide and aluminium chloride both selectively cleaved the MOM group from the ring (generally in almost quantitative yields) without affecting the multiple bonds of the substituent at the 5 position (Scheme 3, Table 2).[14] The best results were obtained working at a temperature of −78°C for boron tribromide and in refluxing dry toluene during 2–3 h for aluminium chloride. In a typical experiment, a 2 M solution of boron tribromide (2.1 mmol) was slowly added under argon to a cold (−78°C) solution of the 2-MOM-pyridazinone **3** (2 mmol) in dry dichloromethane. The mixture was stirred under these conditions for 2 h and a saturated solution of ammonium acetate was added. The mixture was stirred for a further 1 h and the resulting suspension was extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a solid residue that was purified by column chromatography. To cleave the MOM group from pyridazinones bearing an alcohol function we used $AlCl_3$ in order to avoid side reactions due to the brominating properties of

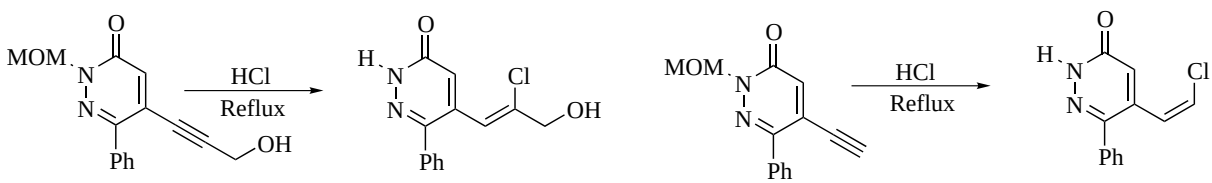


3 **5**

Scheme 3. Method A: $AlCl_3$/toluene, reflux; Method B: (i) BBr_3/CH_2Cl_2 −78°C, (ii) CH_3COONH_4.

Table 1. Palladium-catalysed synthesis of **3a–h** starting from **2**

Compound	Method	R	Yield (%)	Compound	Method	R	Yield (%)
3a	A	$CH{=}CH_2$	90	**3e**	A	C≡C–Ph	88
3b	A	$COCH_3$	80	**3f**	C	Ph	98
3c	B	C≡C–CH_2OH	85	**3g**	A	C≡CH	48
3d	B	C≡C–TMS	75	**3h**	D	CH=CH–Ph	40



3c **4a** **3g** **4b**

Scheme 2.

Table 2. Deprotection of 2-MOM-pyridazinones using Lewis acids

Compound	R	Reagent[a]	Yield (%)	Compound	R	Reagent[a]	Yield (%)
5a	$CH{=}CH_2$	A	93	**5g**[c]	C≡CH	A	90
5b	$COCH_3$	B	95	**5h**	CH=CHPh	A	94
5c[b]	$C{\equiv}C{-}CH_2OH$	A	76	**5i**	CH=CHCOPh	A	97
5d	C≡C–TMS	A	97	**5j**	2-Thienyl	A	98
5e	C≡C–Ph	A	98	**5k**	CH=CHCOOEt	A	97
5f	Ph	A	98	**5l**	CH=CHCN	A	95

[a] Although both reagents were effective in all cases (except **5c**), the best yields were obtained with the listed method.
[b] Only obtained using method A.
[c] Obtained in low yield using BBr_3.

BBr_3 (deprotection of compound **5c** using BBr_3 gave the corresponding bromopropargyl derivative in 76% yield).

In order to test the scope of this approach (in addition to the synthesis of **3a**–**h**) we applied it to the preparation of the 2-MOM-deprotected pyridazinones **5a**–**l** (Scheme 3, Table 2). These experiments also afforded the expected deprotected pyridazinones in high yields.[14,16]

The effects of the compounds obtained on platelet aggregation were assayed by the turbidimetric method.[15] Most compounds showed antiaggregation activity in the micromolar or submicromolar range; the most active compounds were **5i** and **5k**. Preliminary results of pharmacological studies concerning the mechanisms of action of these compounds suggest that they inhibit platelet function due to their ability to stimulate the phosphorylation of certain amino acids on the platelet surface. Further studies are in progress in our laboratory to determine in greater detail the structural requirements for antiplatelet agents aimed at this new target.

In conclusion, we have developed a practical palladium-assisted procedure for the synthesis of MOM-protected pyridazinones and combined this with a convenient selective protocol to perform the MOM-deprotection of such systems bearing acid-sensitive alkenyl or alkynyl substituents. The deprotection method employs Lewis acids under very mild conditions. These procedures have allowed us to prepare a series of novel 3(2*H*)-pyridazinones that inhibit platelet function by what appears to be a previously undescribed mechanism.

References

1. Sotelo, E., Raviña, E., *Synth. Commun.*, accepted for publication.
2. Frank, H.; Heinisch, G. In *Progress in Medicinal Chemistry*; Ellis, G. P.; West, G. B., Eds. Pharmacologically active pyridazines; Elsevier: Amsterdam, 1990; pp. 1–49.
3. Moos, W. H.; Humblet, C. C.; Sircar, I.; Rithner, C.; Weishar, R. E.; Bristol, J. A.; McPhail, A. J. *J. Med. Chem.* **1987**, *30*, 1963–1972.
4. Coates, W. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds. Pyridazines and their benzo derivatives; Pergamon Press, 1996; pp. 1–1183.
5. Greene, T.; Wust, G. P. M. *Protective Groups in Organic Synthesis*, 3rd ed; Wiley: New York, 1999; p. 632.
6. Laguna, R.; Rodriguez-Liñares, B.; Cano, E.; Estévez, I.; Raviña, E.; Sotelo, E. *Chem. Pharm. Bull.* **1997**, *45*, 1151–1156.
7. Montero-Lastres, A.; Fraiz, N.; Cano, E.; Laguna, R.; Estévez, I.; Raviña, E. *Biol. Pharm. Bull.* **1999**, *22*, 1376–1379.
8. Raviña, E.; Terán, C.; Santana, L.; García Domínguez, N.; Estévez, I. *Heterocycles* **1990**, *31*, 1967–1974.
9. Sotelo, E.; Raviña, E.; Estévez, I. *J. Heterocyclic Chem.* **1999**, *36*, 985–990.
10. Estévez, I.; Coelho, A.; Raviña, E. *Synthesis* **1999**, *9*, 1666–11670.
11. Coelho, A.; Sotelo, E.; Estévez, I.; Raviña, E. *Synthesis* **2001**, *6*, 871–876.
12. Meyers, A. I.; Durandetta, J. L.; Munavu, R. *J. Org. Chem.* **1975**, *40*, 2025–2029.
13. Selected physical and spectral data for compounds **4a** and **4b**. Compound **4a**: Yield: 90%, mp 146–147°C (dec.), *iso*-PrOH. IR (KBr): 3808–3065, 1663, 1590 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 4.02 (s, 1H, CH), 6.58 (s, 1H, CH), 7.06 (s, 1H, CH), 7.42 (m, 5H, arom.), 13.26 (brs, 1H, NH). HRMS, *m*/*z*: calcd. for $C_{13}H_{11}ClN_2O_2$ (M^+) 262.0509, found 262.0521. Compound **4b**: Yield: 90%, mp 175–176°C (dec.), *iso*-PrOH. IR (KBr): 3903–3648, 1661, 1589 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 6.31 (dd, 1H, $J=8.3$ Hz, 1H, CH), 6.53 (dd, 1H, $J=8.3$ Hz, CH), 7.42 (m, 5H, arom.), 7.47 (s, 1H, CH), 13.04 (brs, 1H, NH). HRMS, *m*/*z*: calcd. for $C_{13}H_9ClN_2O_2$ (M^+) 232.0403, found 232.0410.
14. Selected physical and spectral data for representative compounds. Compound **5a**: Yield: 97%, mp 169–170°C. IR (KBr): 1669, 1092 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 5.50 (d, 1H, $J=10.9$ Hz, $CH{=}CH_2$), 5.87 (d, 1H, $J=17.2$ Hz, $CH{=}CH_2$), 6.45 (dd, 1H, $J=10.9$, 17.2 Hz, $CH{=}CH_2$), 7.11 (s, 1H, CH), 7.43 (m, 5H, arom.), 12.68 (brs, 1H, NH). Compound **5b**: Yield: 95%, mp 191–192°C, *iso*-PrOH. IR (KBr): 1702, 1668 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 2.14 (s, 3H, CH_3), 7.02 (s, 1H, CH), 7.43–7.46 (s, 5H, arom.), 12.64 (brs, 1H, NH). Compound **5c**: Yield: 76%, mp 200°C, AcOEt. IR (KBr): 3100, 1680 cm^{-1}. ^1H NMR (MeOD, 300 MHz): 3.34 (t, 1H, $J=1.6$ Hz, OH), 4.35 (s, 2H, CH_2), 7.16 (s, 1H, CH), 7.47 (m, 3H, arom.), 7.75 (m, 2H, arom.), 13.18 (brs, 1H, NH). Compound **5e**: Yield: 90%, mp 292–293.4°C, *iso*-PrOH. IR (KBr): 3854, 3672, 1647 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): 4.79 (s, 1H, CH), 7.18 (s, 1H, CH), 7.44 (m, 3H, arom.), 7.62 (m, 2H, arom.), 13.35 (brs, 1H, NH). Compound **5g**:

Yield: 96%, mp 222.0–222.8°C, acetonitrile. IR (KBr): 3124, 1664 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 6.97 (s, 1H, CH), 7.05 (d, 2H, $J=8.4$ Hz, arom.), 7.16 (d, 2H, $J=8.4$ Hz, arom.), 7.30–7.40 (m, 5H, arom.), 11.65 (brs, 1H, NH).

15. Born, G. V. R. *Nature* **1962**, *194*, 927–932.
16. Complete details of the synthesis, spectral characteristics and biological evaluation of the compounds obtained will be published elsewhere in a full paper. All compounds gave satisfactory microanalytical data (C, H, N±0.4%) and spectral data (^1H, ^{13}C, FTIR, MS). Yields given correspond to isolated pure compounds.