Pergamon

Tetrahedron Letters 41 (2000) 2863–2866

TETRAHEDRON LETTERS

Pyridazines. Part 22:[1] Highly efficient synthesis of pharmacologically useful 4-cyano-6-phenyl-5-substituted-3(2*H*)-pyridazinones

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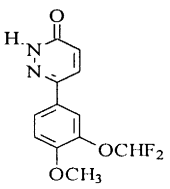
Received 21 January 2000; accepted 9 February 2000

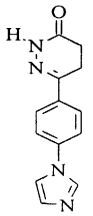
Abstract

A cyano group was directly and efficiently attached at the 4-position of the heterocyclic ring of 5-substituted-6-phenyl-3(2*H*)-pyridazinones using a practical and mild procedure. This direct cyanide addition offers a novel and one-pot approach to the synthesis of pharmacologically useful 4,5-difunctionalized-6-phenyl-3(2*H*)-pyridazinones.

The 6-aryl-3(2*H*)-pyridazinones have attracted particular attention due to their biological activity, most of them related to the cardiovascular system. In this field several compounds such as zardaverine or imazodan have been developed as PDE III inhibitors in the search for new antiplatelet or cardiotonic agents.[2] In recent years the potent platelet inhibitor activity of several 6-phenyl-4,5-disubstituted-3(2*H*)-pyridazinones has been reported.[3] Synthetic approaches to these compounds, which are attractive synthetic building blocks for the preparation of diverse compounds of biological interest,[4] usually involve nucleophilic substitution of 4,5-dihalopyridazinones[5] or oxidative cleavage of bicyclic compounds.[6]



Zardaverine



Imazodan

Considerably fewer methods based on the direct introduction of a substituent at the 4-position of 5-substituted-3(2*H*)-pyridazinones have been described and these methods used as starting materials *N*-protected pyridazinones having barely or no removable protecting group.[7] The direct and regiospecific

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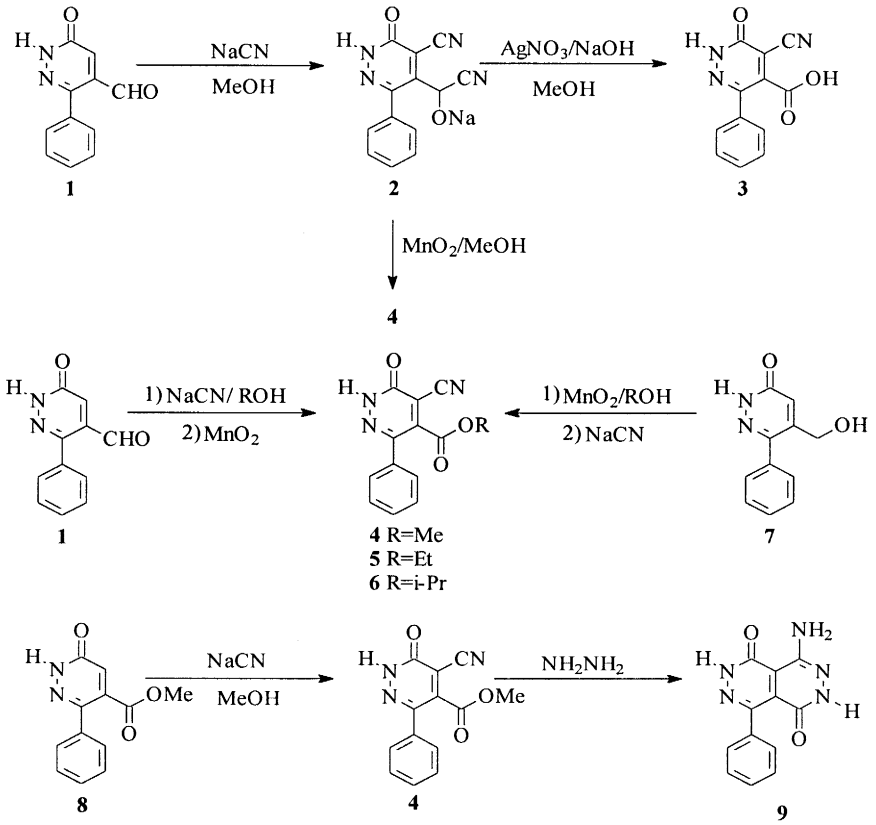
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00260-4

amination at the 4-position of 6-aryl-3(2*H*)-pyridazinones has been reported, but this reaction is highly sensitive to steric factors and the presence of a substituent at the 5-position causes a marked reduction in the reaction rate.[8] Therefore, methods for direct introduction of substituents into the pyridazinone ring are lacking and new developments are of great interest because they should provide access to a wider variety of 4,5-disubstituted compounds.

Several years ago we were interested in the platelet inhibitory activity of a series of 6-aryl-3(2*H*)-pyridazinones substituted at the 5-position with a non-c-AMP PDE III-based mechanism.[9,10] In this field, we have recently described some new findings on the mechanism of the action of these compounds.[11,12]

In a program aimed at developing simple and efficient syntheses of pharmacologically useful pyridazinones, we report here a practical and efficient synthetic strategy to obtain some novel 4-cyano-6-phenyl-5-substituted-3(2*H*)-pyridazinones by direct and regiospecific cyanuration at the 4-position of the heterocyclic ring starting from 6-phenyl-3(2*H*)-pyridazinones substituted at the 5-position.

As part of our detailed study of the reactivity of the 5-formyl-6-phenyl-3(2*H*)-pyridazinone **1**, we obtained their cyanhydrine in 90% yield by treatment of the aldehyde with an excess of sodium cyanide in methanol (Scheme 1). The analysis of the spectroscopic and analytical data of the isolated compound showed the formation of the cyanhydrine **2** which has a cyano group at the 4-position. This result, which could be explained on the basis of the conjugate addition of the cyanide anion to the α,β-unsaturated system present at the 4,5-positions of the aldehyde **1** (following the sequence 1,4-addition–1,2-addition), has important preparative applications to the synthesis of the novel and highly functionalized 3(2*H*)-pyridazinones.



Scheme 1.

Taking this result as a reference, we have studied several transformations that use a cyanhydrine as a reactive intermediary. One of the best known of these procedures is the preparation of carboxylic acids by oxidation of cyanhydrines. The selective action of silver oxide (obtained by addition of sodium hydroxide to silver nitrate) on the hydroxylic function present at the 5-position of the cyanhydrine **2**, prepared as described initially, provides an excellent preparative method to obtain the 5-carboxy-4-cyano-6-phenyl-3(2*H*)-pyridazinone **3** as a crystalline solid in 88% yield, due to the nucleophilic attack of the hydroxyl ion to the acylcyanure intermediate.

Another important procedure that involves cyanhydrin formation is the one-pot three-step transformation of α,β-unsaturated aldehydes into the corresponding methyl esters,[13] by using manganese dioxide and sodium cyanide, reported in 1968 by Corey et al. This method was recently modified to avoid the effect of the acid medium on polyfunctional substrates.[14] The formation of the ester group takes place without isolation of the cyanhydrin which is oxidized to an activated acylcyanide, which, in turn, experiments an alcoholysis by the solvent. Following these references, we performed the oxidation of the cyanhydrin **2** with manganese dioxide in methanol, obtaining 4-cyano-5-methoxycarbonyl-6-phenyl-3(2*H*)-pyridazinone **4** in high yield (95%) as a yellow crystalline solid (m.p. 190.2–191°C, *iso*-PrOH). This compound is also obtained in one-pot by reaction of the aldehyde **1** with sodium cyanide and manganese dioxide in methanol at room temperature. Under these mild conditions and using ethanol or isopropyl alcohol as a solvent, we efficiently extended this procedure to obtain compounds **4** and **5** with yields ranging from 85 to 90%. The novel compounds **3**, **4** and **5** are also versatile intermediates in the preparation of other 4,5-disubstituted-3(2*H*)-pyridazinones or in the synthesis of heterobicyclic compounds.

In a typical experiment, to a solution of the aldehyde **1** (2 mmol) in 30 ml of the required alcohol, was added in several portions an excess of sodium cyanide (3 equiv,). After 10 min of stirring, manganese dioxide (15 equiv,) was added and the mixture was stirred at room temperature for 12 h, filtered out through silica gel and the solvent evaporated in vacuo to obtain the 4,5-substituted-3(2*H*)-pyridazinone which was purified by recrystallization from isopropanol.

In concordance with our previous papers where aldehyde **1** is prepared by oxidation of the corresponding allylic alcohol using manganese dioxide,[10] and taking into account the high reactivity of this reagent in the oxidation of allylic alcohols in the presence of different alcohols, we have obtained compounds **3** and **4** in a very simple one-pot procedure by simultaneous addition of manganese dioxide and sodium cyanide to a solution of the alcohol **6** in the appropriate alcohol at room temperature over 48 h.

With the aim to explore the synthetic possibilities of applying this result to other 6-phenyl-3(2*H*)-pyridazinones having an electron-withdrawing group at the 5-position, we studied the reaction of 6-phenyl-5-methoxycarbonyl-3(2*H*)-pyridazinone **7**, prepared as previously described,[10] with sodium cyanide, obtaining, after 36 h of stirring at room temperature in methanol, compound **2** in 70% yield.[15] This result confirms the 1,4-addition of the cyanide ion to the α,β-unsaturated system present in compounds **1** and **7**. The cyclocondensation of 4-cyano-5-methoxycarbonyl-6-phenyl-3(2*H*)-pyridazinone **4** with hydrazine hydrate at reflux of methanol provides a simple and efficient entry to the pyridazino[4,5-*d*]pyridazine ring system (compound **9**).[16]

The effect of compounds **2**–**6** on platelet aggregation was measured on washed platelets according to the turbidimetric method.[17] All the compounds studied showed high activities in the micromolar or submicromolar ranges and they were more potent than their 5-substituted analogues. New advances on the study of the mechanism of action of this series are still in progress and will be reported elsewhere.

In conclusion, we have developed a highly efficient and practical one-pot synthesis of several pharmacologically useful 4-cyano-6-phenyl-5-substituted-3(2*H*)-pyridazinones. The application of this procedure to other 6-phenyl-3(2*H*)-pyridazinones having electron-withdrawing groups at the 5-position

and the study of different nucleophilic agents able to produce a similar addition at the 4-position on the 3(2*H*)-pyridazinone system are currently being investigated.

Acknowledgements

Financial support of this work by the Xunta de Galicia (Project XUGA 8151389) is gratefully acknowledged. We also thank the Spanish Instituto de Cooperación Iberoamericana for a Doctoral Fellowship to Eddy Sotelo.

References

1. Pyridazines. Part 21: Synthesis and structural study of novel 4-aryl-2,5-dioxo-8-phenylpyrido[2,3-*d*]pyridazines. Pita, B.; Sotelo, E.; Súarez, M.; Raviña, E.; Ochoa, E.; Verdecia, Y.; Novoa, H.; Blaton, N.; De Ranter, C.; Peters, O. M. *Tetrahedron* **2000**, *56*, 2473–2479.
2. Curran, W. V.; Ross, A. *J. Med. Chem*. **1974**, *17*, 273–280.
3. Dal Piaz, V.; Cianini, G.; Turco, G.; Giovannoni, P.; Mideli, M.; Pirisino, R.; Pereeti, M. *J. Pharm. Sci*. **1991**, *80*, 341–348.
4. Dal Piaz, V.; Ciciani, G.; Giovannoni, P. *Acta Chim. Slov*. **1994**, *41*, 189–203.
5. Matyus, P.; Czakó, K. *Trends in Heterocyclic Chemistry* **1993**, *3*, 249–264.
6. Dal Piaz, V.; Ciciani, G.; Turco, G. *Synthesis* **1989**, 213–216.
7. Matyus, P.; Fuji, K.; Tanaka, K. *Heterocycles* **1994**, *37*,171–174.
8. Singh, B.; *Heterocycles* **1984**, *22*, 1801–1805. Badger, E.; Moos, W. H. *J. Heterocyclic Chem*. **1986**, *23*, 1515–1517.
9. Estevez, I.; Raviña, E.; Sotelo, E. *J. Heterocyclic Chem*. **1998**, *35*, 1421–1428.
10. Sotelo, E.; Raviña, E.; Estevez, I. *J. Heterocyclic Chem*. **1999**, *36*, 985–990.
11. Laguna, R.; Rodriguez-Liñares, B.; Cano, E.; Estevez, I.; Raviña, E.; Sotelo, E. *Chem. Pharm. Bull*. **1997**, *45*, 1151–1156, and references cited therein.
12. Montero-Lastres, A.; Fraiz, N.; Cano, E.; Laguna, R.; Estevez, I.; Raviña, E. *Biol. Pharm. Bull*. **1999**, *22*, 1376–1379.
13. Corey, E. J.; Gilman, N. M.; Ganem, B. E. *J. Am. Chem. Soc*. **1968**, *90*, 5616–5617.
14. Lai, G.; Anderson, W. K. *Synthetic Commun.* **1997**, *27*, 1281–1283.
15. Selected physical and spectral data for the obtained compounds. Compound **2**: 90%, m.p. 190.2–191°C (desc.), *iso*-PrOH; IR (KBr): 3808–3065, 1663, 1590 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): 13.94 (brs, 1H, NH), 7.55–7.48 (m, 5H, aromatics), 4.02 (s, 1H, CH) ppm; HRMS *m*/*z* calcd for $C_{13}H_7N_4NaO$ (M^+): 274.0467; found: 274.0491. Compound **3**: 88%, m.p. 253–255°C, *iso*-PrOH; IR (KBr): 3000, 1688, 1650, 1590; ^1H NMR (DMSO-d_6, 300 MHz): 13.57 (brs, 1H, NH), 7.43 (m, 5H, H_{arom}), 7.17 (brs, 1H, COOH). Compound **4**: 95%, m.p. 190.2–191°C, *iso*-PrOH; IR (KBr): 1735, 1668, 1588 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): 14.36 (brs, 1H, NH), 7.50 (m, J=7.91 Hz, 3H, H_{arom}), 7.40 (m, J=7.91 Hz, 2H, H_{arom}), 3.76 (s, 3H, OCH_3) ppm. Compound **5**: 95%, m.p. 181.8–182.5°C, *iso*-PrOH; IR (KBr): 1720, 1666, 1569 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): 14.35 (brs, 1H, NH), 7.48–7.44 (m, 5H, H_{arom}), 4.26 (q, J=7.10 Hz, 2H, OCH_2) 1.02 (t, J=7.10 Hz, 3H, CH_3) ppm. Compound **6**: 93%, m.p. 184–186°C, *iso*-PrOH; IR (KBr): 1731, 1669, 1587 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): 14.34 (brs, 1H, NH), 7.49 (m, 5H, H_{arom}), 5.04 (m, J=6.00 Hz, 1H, CH) 1.11 (d, J=6.00 Hz, 6H, CH_3) ppm. Compound **9**: 90%, m.p. 292–293.4°C, *iso*-PrOH; IR (KBr): 3854, 3672, 1647 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): 13.01 (brs, 1H, NH), 12.18 (brs, 1H, NH), 7.36 (m, 5H, H_{arom}), 6.85 (s, 2H, NH_2).
16. Complete details about the synthesis, spectral data and biological evaluation will be published elsewhere in a full paper. Compounds **3**, **4**, **5**, **6** and **9** gave satisfactory microanalytical (C, N, H±0.4%) and spectral data. The structure of the synthesized compounds can be easily confirmed by the absence of the H_4 signal in the ^1H NMR spectrum.
17. Born, G. V. R. *Nature* **1962**, *194*, 927–932.