Full Research Paper

The tert-amino effect in heterocyclic chemistry: Synthesis of new fused pyrazolinoquinolizine and 1,4-oxazinopyrazoline derivatives

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Abstract

The synthesis of novel fused heterocycles is based on reactions proceeding by the mechanism of the tert-amino effect, which generalizes cyclization of certain derivatives of 3-methyl-1-phenyl-2-pyrazolin-5-ones. Using this strategy a variety of fused heterocycles is obtained by the Knoevenagel condensation of 5-tert-amino-3-methyl-1-phenylpyrazolone-4-carboxaldehyde with active methylene compounds such as malononitrile and cyanoacetamide followed by cyclisation using anhydrous zinc chloride.

Background

The N-phenyl-3-substituted 5-pyrazolone derivatives are organic compounds that have been known since 1883; they are very useful as intermediates for pharmaceuticals and are used as anti-inflammatory agents and allergy inhibitors.[1] Also, these 5-pyrazolone derivatives were investigated as thermal stabilizers for rigid PVC.[2,3] Therefore, large efforts have been directed towards the synthetic manipulation of pyrazolone derivatives to find more useful compounds.[4] In the heterocyclic area, chloroformylpyrazoles of type 2 are interesting starting materials for two reasons: firstly, the chlorine atom is easily substituted by nucleophiles; and secondly, the aldehyde functionality is ideally suited for conversion into a series of active functionalities. The final step (i.e conversion of 4 to 6) is the intramolecular cyclization to provide the condensed heterocyclic system. In our continued interest in the development of highly expedient methods for the synthesis of diverse heterocyclic compounds of biological significance [5-7] we report herein the synthesis of some novel classes of fused pyrazolinoquinolizine and 1,4-oxazinopyrazoline derivatives by exploring the α-cyclization of tertiary amine reaction strategy.

The term tert-amino effect was coined by Meth-Cohn and Suschizky [8] to generalize cyclization reactions of certain ortho-substituted N,N-dialkylanilines. This effect has been observed in ortho-substituted tertiary anilines, especially when ortho-vinyl-substituted anilines have been employed. In general, the ring-closure process leads to five and six membered rings. [9-11] Ring closure of ortho-substituted N,N-dialkylaniline derivatives can proceed in three different ways, depending on the nature of A = B. The first path (a) involves ring closure between the ortho-substituent and the tert-nitrogen atom. The second path (b) comprises those reactions which involve one of the α-methylene groups attached to the atom A, ultimately leading to the formation of five membered rings. The third path (c) involved an analogous reaction of methylene groups and atom B which lead to the formation of six-membered rings. The first reaction of this type was reported in 1895 by Pinnow.[12] Most of the early exam-
amples of the reaction of compounds with an unsaturated ortho-substituent involve groups with at least one heteroatom, such as nitroso,[13] nitro,[14,15] azo,[16] amine,[17] azomethine, [18-20] carbonyl, [20-23] or thiocarbonyl moieties as the ortho substituents.[24] The application of the tert-amino effect to the synthesis of pyrido-fused benzenes, pyridazines and uracils has also been reported. [25-28] In this approach the ring closure occurs between the β-carbon of a vinylic group possessing electron withdrawing substituents at the β-position and the α-carbon of an ortho-tert-amino group. In a recent report this ring closure method is also extended to the preparation of new spirocyclic ring systems by incorporating the β-substituents of the vinylic group into a ring [29] in this way.

Results and discussion

The model compound used in this work was 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde 2 which has previously been prepared by chloroformylation of pyrazoline 1 under Vilsmeier conditions.[29] The 5-chloro atom of 2 is readily displaced by nucleophiles [30-32] and hence the reaction with several cyclic sec-amines (viz pyrrolidine, piperidine and morpholine) resulted in smooth conversion to the 5-tert-amino derivatives 3. These were then used in the Knoevenagel condensation reactions with malonodinitrile to give the corresponding pyrazolinoquinolizines 6a and 1,4-oxazinopyrazolines 6e in refluxing toluene (Scheme 1). The structure of the compound thus obtained was identified from the spectroscopic data and elemental analysis (see Additional File 1 & 2 for full experimental and spectral data). The IR spectrum exhibited a sharp band at 2337 cm\(^{-1}\) (CN). The \(^1\)H NMR spectra showed the absence of the olefinic proton and the presence of a methyl group at δ 2.08 as a singlet. The other signals appeared at δ 1.28 (m, 4H), 3.07 (d, 1H, \(J = 15.4\) Hz), 3.32 (m, 1H), 3.43 (dd, 1H, \(J = 13.7, 6.8\) Hz), 3.67 (m, 1H), 3.86 (m, 1H), 3.98 (m, 1H), 6.68 (br, NH), 7.43 (m, 3H), 7.59 (d, 2H, \(J = 8.6\) Hz). The mass spectrum revealed a strong molecular ion peak at 335 (M\(^+\)). It is to be noted that in the end product 6a one nitrile group is reduced to the corresponding amide group. But it is not yet clear why only one nitrile group is reduced and the other remains intact under the reaction conditions. Similarly, when cyanoacetamide was reacted in place of malonodinitrile and the Knoevenagel product 4b thus obtained was further heated in the presence of zinc chloride, the corresponding pyrazolinoquinolizine 6a was obtained in 60% yield.

The structures of the end products obtained were characterized fully by high resolution spectral analysis (see Additional File 1 & 2 for full experimental and spectral data). We then reacted chloroformyl pyrazolone 2 with pyrrolidine and morpholine to get the corresponding tert-amino derivatives 3. The olefinic products 4 thus obtained from 3, were then cyclized intramolecularly in the presence of zinc chloride to produce the corresponding quinolizines 6 in good yields (Table 1). Although, we could not isolate any intermediates, the reaction proceeds with the Knoevenagel products 4 in the rate determining step undergoing a \(1,5-[H]\) shift prior to cyclization to yield a 6-membered ring product 6 (Scheme 2). This is in contrast to an earlier report by Sandhu et al. to obtain pyrrolo[2,3-d]pyrimidines from 6-tert-amino-substituted uracils and dimethyl acetylenedicarboxylate,[33] However, further work is in progress to understand the exact mechanism of the reaction.
Conclusion
In conclusion, we have demonstrated that N-phenyl-3-substituted pyrazolones can be used for the intramolecular alpha-cyclisation of tertiary amines [34] for the synthesis of pyrazolinoquinolizine and 1,4-oxazinopyrazoline derivatives in good yields.

Table 1: Physical characteristics of pyrazolinoquinolizines and 1,4-oxazinopyrazolines 6

| Entry | Knoevenagel Products | Fused pyrazolines 6 | Reaction times, h | Yields, % | Mp, °C |
|-------|----------------------|---------------------|-----------------|----------|-------|
| 1     | ![Image](image1.png)  | ![Image](image2.png) | 5               | 63       | 140–142 |
| 2     | ![Image](image3.png)  | ![Image](image4.png) | 5               | 60       | 140–142 |
| 3     | ![Image](image5.png)  | ![Image](image6.png) | 12              | 60       | 99–101  |
| 4     | ![Image](image7.png)  | ![Image](image8.png) | 12              | 57       | 99–101  |
| 5     | ![Image](image9.png)  | ![Image](image10.png) | 10              | 55       | 225–226 |
| 6     | ![Image](image11.png) | ![Image](image12.png) | 12              | 43       | 224–226 |

Additional material

Additional file 1
Full experimental data. Experimental procedures and data. Click here for file [http://www.biomedcentral.com/content/supplementary/1860-5397-3-43-S1.doc]

Additional file 2
Supplementary information of compounds. Full data for compounds. Click here for file [http://www.biomedcentral.com/content/supplementary/1860-5397-3-43-S2.doc]
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References

1. Huang FC: U.S. Pat. 4, 668, 694 (1987). Chem Abstr 1987, 107:3927.
2. Sabas MW, Oraby EH, Abdul Naby AS, Mohamed RR: Polym Degrad Stab 2006, 91:911.
3. Sabas MW, Oraby EH, Abdel Naby AS, Mohamed RR: J Appl Polym Sci 2006, 101:1544.
4. L'abbe G, Emmers W, Dehaen W, Dysall LK: J Chem Soc Perkin Trans I 1994:2553.
5. Prajapati D, Gohain M, Thakur Aj: Bioorg Med Chem Lett 2006, 16:3537.
6. Prajapati D, Thakur Aj: Tetrahedron Lett 2005, 43:1433.
7. Prajapati D, Gadhwal S: Tetrahedron 2004, 60:4909.
8. Meth-Cohn O, Suschitzky H: Adv Heterocycl Chem 1972, 14:211.
9. Nijhuis HN, Lena GRB, Reinhoudt DN: Rec Trav Chim Pays-Bas 1989, 108:172.
10. Verboom W, Reinhoudt DN: Rec Trav Chim Pays-Bas 1990, 109:311.
11. Kelderman E, Noorand-Bunt HG, van Eerden J, Verboom W, Reinhoudt DN: Rec Trav Chim Pays-Bas 1991, 110:115.
12. Pinnov J: Ber. Dtsch Chem Ges 1895, 28:3039.
13. Seebach D, Enders D: Angew Chem 1975, 87:1.
14. Fielden R, Meth-Cohn O, Suschitzky H: J Chem Soc Perkin Trans I 1973:696.
15. Gluhareva TV, Morzerherin VS, Mokrushin VS: Chem Heterocycl Comp (Engl Trans1) 2000, 36:107.
16. Kirschke K, Moller A, Schmitz E, Kuban RJ, Schulz B: Tetrahedron Lett 1986, 27:4281.
17. Martin J, Meth-Cohn O, Suschitzky H: Tetrahedron Lett 1973:4495.
18. Tea Gokou C, Pradere JP, Qiuioniu H: Synth Commun 1986, 16:79.
19. Akib 2001, Kosugi Y, Takada T: J Org Chem 1978, 43:4472.
20. Suschitzky H, Walronde RE, Hull R: J Chem Soc Perkin Trans I 1977:47.
21. Falci KJ, Franck RW, Smith GP: J Org Chem 1977, 42:3317.
22. Fokin EP, Russikikh VV: Zhur Org Khim 1966, 2:907.
23. Nijius WHN, Verboom W, Harkema S, Reinhoudt R: Rec Trav Chim Pays-Bas 1989, 108:147.
24. Verboom W, Reinhoudt DN: Rec Trav Chim Pays-Bas 1990, 109:311.
25. Matyus P, Fuji K, Tanaka K: Heterocycles 1994, 37:171.
26. Tverdokhlebov AV, Gorulya AP, Tolmachev AA, Kostyuk AN, Chernega NA, Rusanov EB: Synthesis 2005:395.
27. Meth-Cohn O: Adv Heterocycl Chem 1996, 65:1-37.
28. D'yachenko EV, Gluhareva TV, Nikolayenko EF, Tkachev AV, Morzerherin YY: Russ Chem Bull 2004, 53:1240.
29. Schwartz A, Beke G, Kovari Z, Bocsky Z, Farkas O, Matyus P: Theor Chim 2000, 528:49-57.
30. Senda S, Hirota K, Yang G, Shirhashi M: Yakugaku Zasshi 1971, 91:1372. Chem. Abst. 1973, 79: 105284.
31. Wamhoff H, Dzienis J, Hirota K: Adv Heterocycl Chem 1992, 55:129.
32. Prajapati D, Sandhu JS: Synthesis 1988:342.
33. Bhuyan PJ, Sandhu JS, Ghosh AC: Tetrahedron Lett 1996, 37:1853.
34. Matyus P, Elias O, Tapolcsanyi P, Polonika-Balint A, Halasz-Dajka B: Synthesis 2006:2625.