Tetrahedron Letters, Vol 32, No 39, pp 5375-5378, 1991
Printed in Great Britain

0040-4039/91 $3 00 +
Pergamon Press plc

The Reaction of Malononitrile with Chalcone: A Controversial Chemical Process

Pedro Victory*, José I. Borrell, Anton Vidal-Ferran

Departament de Química Orgànica, CETS Institut Químic de Sarrià (Centre Associat CSIC), E-08017 Barcelona, Spain

and

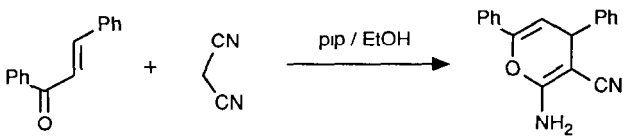
Carlos Seoane, José L. Soto

Departamento de Química Orgánica, Universidad Complutense, E-28040 Madrid, Spain.

Key Words: Versatile Michael addition, 2-aminoisophthalonitrile, hexasubstituted cyclohexanol, 4H-pyran, 3-cyanopyridine.

Abstract: *Given the significant discrepancies in the several reported results on the reaction of chalcone (1,3-diphenyl-2-propen-1-one) (1) with malononitrile (2), a careful reinvestigation was carried out. Depending upon the reaction conditions either the open-chain Michael adduct (4), an alkoxypyridine (5), an aminoisophthalonitrile (6) or a cyclohexanol (7) is obtained. However, no 4H-pyran could be isolated from this reaction.*

In a paper recently published in this journal[1] by Tyndall *et al.*, a structure of 4*H*-pyran (**3**) was proposed for the product obtained from the reaction of chalcone (**1**) with malononitrile (**2**) in ethanol using piperidine (pip) as catalyst (Scheme 1).



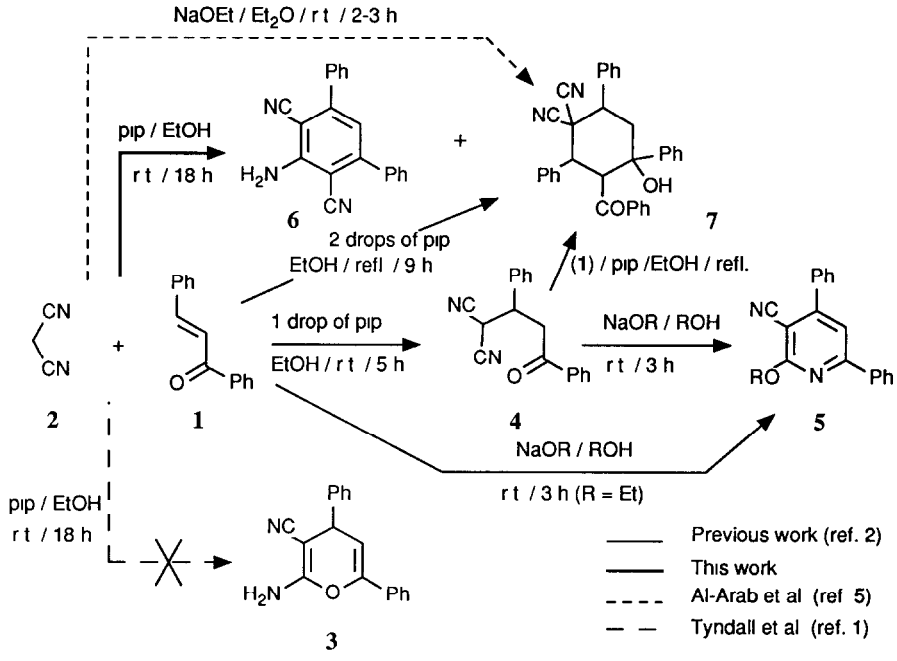
1 **2** **3**

Scheme 1

This result is clearly in conflict with previous results on this reaction[2], as malononitrile was reported to react with chalcone to give the open chain Michael adduct (**4**) in mild basic conditions and alkoxypyridines (**5**) if an alkoxide is used (Scheme 2).

These significant discrepancies and our extensive work on the synthesis of 4*H*-pyrans prompted us to carefully reinvestigate the work reported by Tyndall[1] *et al*

As a result of this reinvestigation we want to report now that the reaction of malononitrile with chalcone (**1**) by using the Tyndall *et al.* procedure yields a mixture of two compounds. None of them corresponds to the proposed 4*H*-pyran (**3**). Instead the 2-aminoisophthalonitrile (**6**)[3] and the cyclohexanol (**7**)



Scheme 2

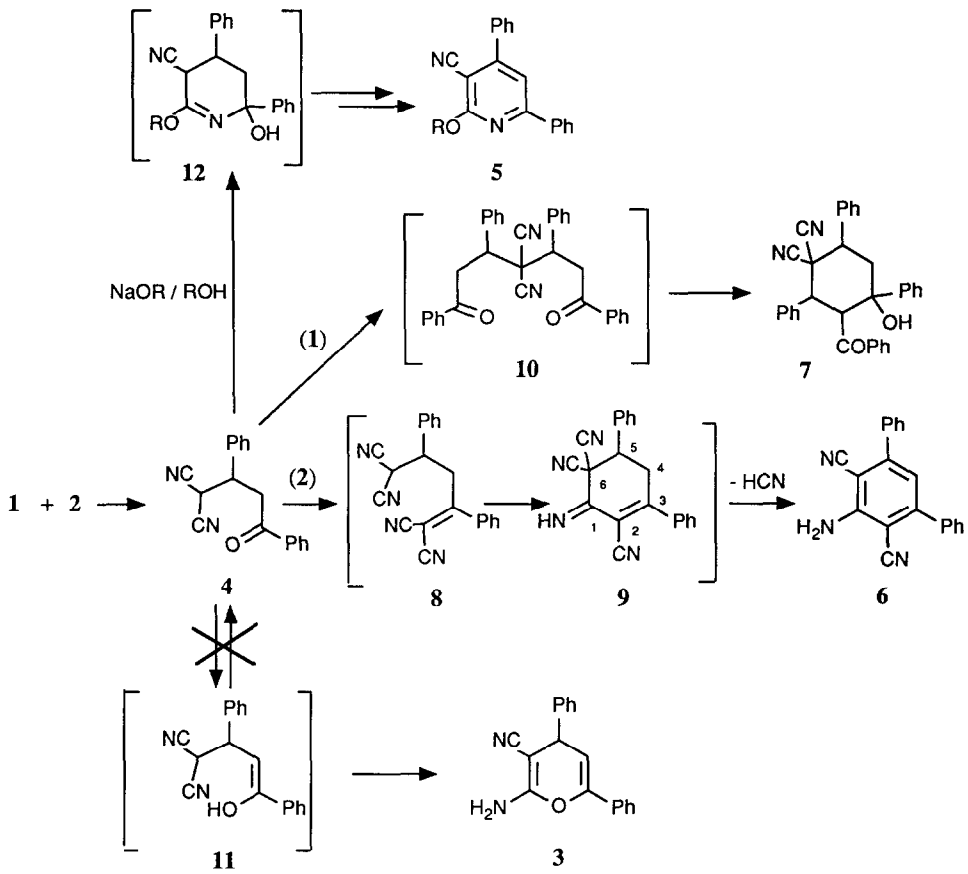
have been obtained[4]. (**7**) was previously described by reaction of (**1**) and (**2**) using two drops of piperidine in ethanol at reflux[2] during 9 h. (**7**) was also obtained when 2-cyano-5-oxo-3,5-diphenylpentanonitrile (**4**) [formed by addition of (**1**) and (**2**) in ethanol at room temp. with one drop of piperidine[2]] was treated with chalcone in ethanolic piperidine at reflux (Scheme 2). Al-Arab *et al.* have also described the synthesis of (**7**) using $NaOEt/Et_2O$ instead of piperidine/ethanol[5].

Neither of the above experimental conditions afforded the 4*H*-pyran (**3**) described by Tyndall *et al* Furthermore, the presence in the IR spectrum reported in their paper of a sole amino absorption band and the very high position of the cyano stretching band (2260 cm^{-1}) do not support the proposed structure. Even the formation of a significant amount of (**3**) in the reaction mixture could be questioned because the ^{13}C NMR spectra of the crude solids isolated from the mother liquors, after removing the main compounds, did not show any signal in the range 50-60 ppm[6].

The results reported in this work can be rationalized by the mechanistic hypothesis depicted in Scheme 3. In any case the reaction starts with Michael addition of (**2**) to (**1**) yielding the open-chain adduct (**4**). Knoevenagel condensation of (**4**) with a second molecule of malononitrile leads to (**8**)[7] which undergoes cyclization to give (**9**) and HCN elimination to afford the aminoisophthalonitrile (**6**). A similar path has been reported[8] for the formation of a structure related to (**9**) but bearing two substituents at position C-5. Its inability to undergo elimination prevents the aromatization.

Compound (**4**) can also react with a second molecule of (**1**) to give the Michael bis-adduct (**10**), the cyclization of which leads to cyclohexanol (**7**)[9].

Attempts to get heterocyclization in (**4**) require strong basic conditions (NaOR/ROH) but alkoxypyridine (**5**) is obtained inevitably. The 4*H*-pyran was never isolated. Actually, formation of pyran (**3**)



Scheme 3

is not a favoured process as it is known that 4-oxonitriles only cyclize to aminopyrans when the enolic form of the carbonyl group is stabilized by conjugation with a suitable α-located substituent[10]. This is not the case in compound (**4**).

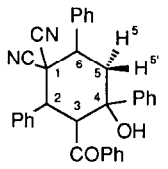
It has to be said that 4*H*-pyran (**3**) has been proposed as an intermediate in the formation of pyridines (**4**) by Al Arab *et al*[11].

Acknowledgement: One of us (A. V.-F.) would like to thank the *Fundació J. Salañer* for a grant.

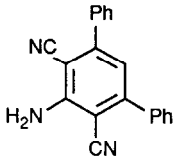
References and Notes

1. Tyndall, D. V.; Al Nakib, T.; Meegan, M. J. *Tetrahedron Lett* **1988**, *29*, 2703.
2. Soto, J. L.; Seoane, C.; Ciller, J. A. *An Quim* **1980**, *76C*, 281; *Chem Abstr.* **94**, 192085.
3. Structure (**6**) was confirmed by comparison with an authentic sample preparated as described by Gewald, K. and Schill, W. *J. Prak Chem* **1971**, *313*, 678.
4. In a typical experiment: 2.1 g (0.01 mol) of chalcone and 0.78 g (0.012 mol) of malononitrile were

disolved in 30 ml of absolute ethanol and 8 ml of piperidine were added dropwise. The mixture was stirred for 18 h at room temp. After removal of the solvent *in vacuo* at room temp., 10 ml of 10 % acetic acid were added and the resulting solid was filtered, washed with water and dried, obtaining 3.04 g. After recrystallization from ethanol, a mixture of the aminoisophtalonitrile (**6**) and the cyclohexanol (**7**) was obtained, which was chromatographed on silica gel Merck 60 (70-230 mesh) using CH_2Cl_2/hexane (1:1) as eluent. Thus, 1.22 g (50.6% based on chalcone) of 3-benzoyl-4-hydroxy-2,4,6-triphenyl-1,1- -cyclohexanedicarbonitrile (**7**) and 0.46 g (15.4% based on chalcone) of 2-amino-4,6-diphenyl- -isophthalonitrile (**6**) were obtained.



7



6

(**7**): m.p. 212-214°C. - IR (KBr): υ = 3417 cm^{-1} (OH), 2253 (C≡N), 1642 (C=O), 1595, 1577, 1496, 1450, 762 and 700 (Ph). - ^1H NMR ($CDCl_3$): δ = 7.05-7.65 ppm (m, 20 H, H-Ph), 5.18 (br. s, 1 H, OH, deuterable), 4.85 (d, *J* = 11.9 Hz, 1H, 3-H), 4.20 (d+d, 2 H, *J* = 12 Hz, 2-H + 6-H), 2.94 (t, 1H, 5-H), 2.26 (dd, 1H, *J* = 14.5 and 3.3 Hz, 5'-H). - ^{13}C NMR ($CDCl_3$): δ = 204.0 ppm (C=O), 124.7-144 (Ph), 113.8 (C≡N), 74.6, 51.8, 50.4, 48.0, 46.3 and 40.9 (cyclohexane carbons). - MS (70 eV): m/z (%): 209 (61.6), 167 (21.0), 131 (14.6), 105 (100), 91 (11.5), 77 (69.3). $C_{33}H_{26}N_2O_2$ (482.6), Calcd. C 82.13, H 5.43, N 5.81. Found C 82.03, H 5.36, N 5.98.

(**6**): m.p. 223-224°C. - IR (KBr): υ = 3475, 3371, 3227 and 1634 cm^{-1} (NH_2), 2213 (C≡N), 1571, 1497, 762 and 697 (Ph). - ^1H NMR (d_6DMSO): δ = 7.56-7.58 ppm (m, 10 H, H-Ph), 6.80 (s, 1 H, 5-H), 6.60 (br. s, 2H, NH_2, deuterable). - ^{13}C NMR (d_6DMSO): δ = 154.1 ppm (C-2), 149.8 (C-4 and C-6), 128.5-137.5 (Ph), 118.7 (C-5), 116 0 (C≡N), 94.3 (C-1 and C-3). - MS (70 eV): m/z (%): 295 (100) [M^+], 294 (18.9), 268 (5.9), 241 (1.7), 214 (1.1). $C_{20}H_{13}N_3$ (295.3), Calcd. C 81.34, H 4.44, N 14.23. Found C 81.49, H 4.37, N 14.01.

5. The very same compounds already reported in 1980 by our group (ref. 2) have been recently reported as new compounds by Al-Arab, M. M.; Tabba, H. D.; Ghanem, B. S.; Olmstead, M. M. *Synthesis* **1990**, 1157.

6. This very high field signal for an ethylenic carbon (C-3) is characteristic of a 3-cyano-2-amino-(4*H*)-pyran: Pascual, C.; Martin, N.; Seoane, C. *Magn. Reson. Chem.* **1985**, *23*, 793.

7. Alternatively, the Knoevenagel condensation can take place as the first step.

8 Martín, N.; Segura, J. L.; Seoane, C., Soto, J. L. *J. Chem. Res (S)* **1990**, 310.

9 In support of the mechanistic proposal, the corresponding bis-adduct can be isolated when the 3-(*p*-chlorophenyl)-1-phenyl-2-propen-1-one is used.

10. Seoane, C.; Soto, J. L.; Quinteiro, M. *Heterocycles* **1980**, *14*, 337; C Seoane, *La química de los 4H-piranos*, Monografías de la Real Academia de Química, Madrid, 1982.

11. Al Arab M. M. *J. Heterocyclic. Chem* **1989**, *26*, 1665.

(Received in UK 15 July 1991)