Tetrahedron Letters 50 (2009) 3050–3053

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient Horner–Wadsworth–Emmons intramolecular cyclisation of a N-substituted phthalimide promoted by KF-Alumina: a general tool for the synthesis of functionalised isoindolinones

Vittorio Pace [a], Fernando Martínez [a], Clara I. Nova [b], María Fernández [a], José Vicente Sinisterra [a,b], Andrés R. Alcántara [a,b,*]

[a] Department of Organic and Pharmaceutical Chemistry, Pharmacy Faculty, Complutense University, Pza. Ramón y Cajal s/n, 28040 Madrid, Spain
[b] Industrial Biotransformations Service (SBI), Scientific Park of Madrid (PTM), C/Santiago Grisolia 2, 28760 Tres Cantos, Madrid, Spain

ARTICLE INFO

Article history:
Received 27 February 2009
Revised 31 March 2009
Accepted 3 April 2009
Available online 14 April 2009

Keywords:
Horner–Wadsworth–Emmons reaction
Isoindolinones
Cyclisation
Heterogeneous catalysis
Enones

ABSTRACT

An intramolecular Horner–Wadsworth–Emmons reaction promoted by KF-Alumina involving a N-substituted phthalimide, cleanly and efficiently furnishes an interesting α,β-unsaturated tricyclic enone which may undergo selective alkylations at the α′-position.

Isoindolinones constitute the core of several natural compounds, such as magallanesine[1] (Fig. 1), an isoindolobenzazocine isolated from the South-American plant *Berberis darwinii*, a pentacyclic nucleus with a characteristic benzazocine ring system in which the nitrogen is present as a vinylogous imide, and could be formally derived by the intramolecular cyclisation of an appropriate phthalimide derivative. Moreover, the interest towards isoindolinones from a medicinal chemistry perspective is prompted because of their presence in 5-HT_{1A},[2a] 5-HT_2,[2a,b] or D_2 antagonists,[2a,b] as well as in antileukemic drugs.[2c]

Considerable efforts have been directed towards the synthesis of isoindolinones (phthalimidines). They have been prepared via Grignard[3] or lithiation[4] procedures, as well as by Diels–Alder cycloadditions,[2c,5] rearrangement[6] and photochemical reactions.[7] The reduction of N-substituted phthalimides[8] and the condensation of phthalaldehyde[9] also afford isoindolinones. In addition, different palladium-catalysed syntheses of isoindolinones have been reported,[10] while, on the other hand, isoindolin-1-ones have also been prepared via electrophilic cyclisation of *o*-(1-alkynyl)benzamides,[3] or by the addition of in situ generated organoalanes to acyliminium ions.[11]

All the methodologies above reported involve the employment of some reagents, such as organometallic compounds, which should be avoided in order to promote an eco-friendlier process, according to modern synthetic chemistry principles; thus, we considered that a Wittig-type process could be more appropriate for preparing such structures.

In fact, the Wittig reaction of compounds different from aldehydes and ketones has been extensively studied;[12] more concretely, Wittig reaction of imides is applicable to intramolecular processes and has been employed in the preparation of a wide range of heterocyclic systems.[13] An useful alternative to classical Wittig reaction is represented by the Horner–Wadsworth–Emmons reaction (HWE),[14] in which the nucleophilic ylid is obtained from a β-ketophosphonate. However, to the best of our knowledge, only a few examples have applied this attractive methodology to imide chemistry, generally reporting low reaction yields.[15] On the contrary, related carbonyl compounds such as lactones, may

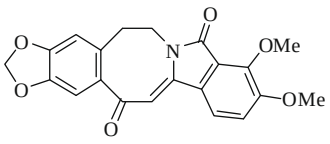


Figure 1. Magallanesine.

* Corresponding author. Tel.: +34 91 3941820; fax: +34 91 3941822.
E-mail address: andresr@farm.ucm.es (A.R. Alcántara).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.029

undergo intramolecular HWE type-condensation, thus providing an useful synthetic route to analogous five-membered ring structures.[16]

In this Letter we wish to report a convenient procedure, based on a HWE intramolecular cyclisation of a β-ketophosphonate **1**, prepared from N-substituted phthalimides, for the construction of the heterofused isoindolinone **2**, namely 2*H*-pyrrolo[2,1-*a*]isoindole-2,5(3*H*)-dione. As can be seen in Scheme 1, mechanism reaction involves the nucleophilic intramolecular addition of carbanion **1a** generated from the phosphonate **1** to the phthalimide carbonyl, followed by spontaneous elimination of phosphate from the oxaphosphetane **1c** and formation of the highly stable α,β-unsaturated cyclic ketone **2**.

Previously, compound **2** has been prepared by flash vacuum pyrolysis (FVP) of stabilized phosphorous ylides under drastic reaction conditions: in particular, performing the cyclisation at 750 °C (as described by Aitken,[17a]) represents a major drawback, because of the severe complexity of reaching those extreme conditions in normal laboratories. Alternatively, Caballero et al. obtained this tricyclic system as an undesired product of the Wittig reaction between a phosphorane and *N*-phenylsulfonylindole-3-carbaldehyde.[17b] Finally, Bestmann and co-workers noticed the formation of pyrroloisoindolediones as the consequence of the intramolecular cyclisation promoted by heating of an appropriate phosphoranylideneketenimine.[17c]

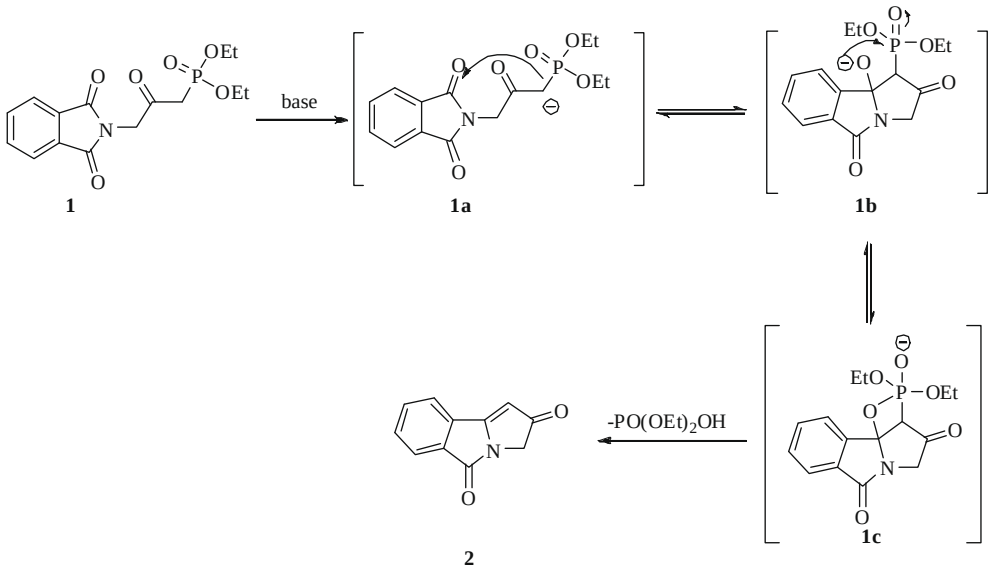
The effective precursor of β-ketophosphonate **1**[18] is 3-phthalimido-1-iodopropan-2-one **4**, easily obtained in quantitative yield by an interesting new route consisting in ring opening of 2,3-epoxypropylphthalimide **3** with concentrated HCl, subsequent oxidation of the resulting chlorohydrine using the Jones reagent and, finally, a Finkelstein process to afford the desired α-iodoketone **4**, which underwent a subsequent Arbuzov reaction[19] to yield phosphonate **1**, as depicted in Scheme 2. It is worth noting that carrying out the Arbuzov reaction on α-iodoketone **4** without solvent under reflux allows eliminating any Perkow side reaction, which usually is obtained along with the desired nucleophilic displacement,[20] so that, under these reaction conditions, we obtained β-ketophosphonate **1** exclusively.

We examined the possibility to promote the cyclisation of the β-ketophosphonate under basic conditions, as depicted in Scheme 1. Table 1 shows the experimental results obtained using different bases. The first choice was supported KF, which had previously allowed us to report high chemoselective procedures in *N*-allylation of anilines.[21] So we checked the viability of the reaction on the β-ketophosphonate by using KF-Alumina.[22] This catalyst had been already employed in such HWE chemistry by different authors,[23] although they described the limitation of its use in classical reactions involving aldehydes and ketones.

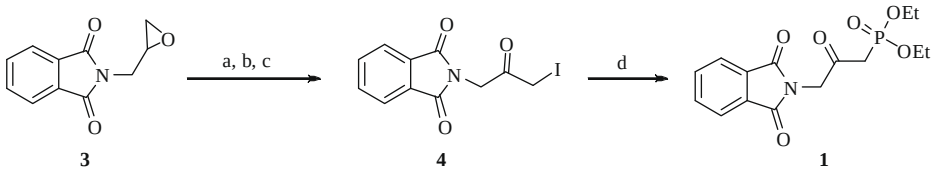
As detailed in Table 1, the best result, 93% of cyclisation product, was obtained under KF-Alumina catalysis at 60 °C in only 1 h. It seemed that solvent effect was not dramatic, since at the same temperature acetonitrile and DMF gave comparable results (entries 1 and 3). Remarkably, by increasing temperature the amount of cyclisation product decreased: this can be explained by the fact that, since reaction is an equilibrium, temperature could shift it towards the open form (entries 1 and 2). Interestingly, the milder basic nature of KF-Celite (entry 4) did not allow to achieve the cyclisation, and furthermore the use of unsupported KF (entry 5) was also ineffective. Ordinary bases used in organic synthesis (^{t}BuOK, NaOMe or NaH) were also effective to promote this transformation in analogous reaction times (entries 6–8) with slightly lower yields. Furthermore, the synthetic utility of the supported catalyst is readily demonstrable.[22,24] All reactions can be carried out cleanly, rapidly and in high yield under mild conditions, whereas attempts to carry out the same reactions with unsupported catalyst frequently either fail or result in the formation of mixture of products. This not only becomes environmentally benign but also offers economically favourable situation as compared to cumbersome and cost-effective separation of the products in corresponding homogeneous procedures.

The simplicity of our reaction conditions led to higher yield of adduct **2** compared to before-mentioned methodologies based on a classical Wittig reaction.[17b,c] More concretely, we have maximised the yield and minimised the reaction time: Bestmann, reported only a 56% of isolated yield of **2** after 12 h.[17c] These results are in excellent agreement with the general higher reactivity of ylids derived from phosphonates towards those obtained from phosphoranes.[25] Furthermore, work-up of HWE reactions is easier compared to that of their Wittig counterparts, as phosphonate esters are soluble in water and elimination of the supported KF is performed simply by filtering the reaction mixture in vacuo.

Of particular synthetic value is the generation of the enolate of the cyclic α,β-unsaturated enone so formed, which may be alkylated selectively at the α′-position of the ketone as described by



Scheme 1. HWE intramolecular cyclisation mechanism.

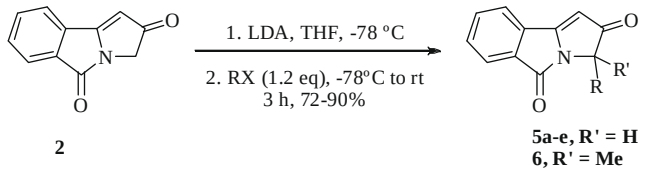


Scheme 2. Preparation of β-ketophosphonate **1.** Reagents and conditions: (a) $CHCl_3$, HCl 37%, 0 °C, 30 min, quant.; (b) CrO_3, acetone 0 °C, 30 min, quant.; (c) NaI, acetone, rt, 2 h, quant.; and (d) $PO(Et)_3$, neat, reflux 4 h, 91%.

Table 1
Cyclisation of β-ketophosphonate promoted by different bases via Scheme 1

Entry	Cyclisation product[a] (%)	Conditions
1	93	KF-Alumina (1.0 equiv), MeCN, 60 °C, 1 h
2	70	KF-Alumina (1.0 equiv), MeCN, 82 °C, 1 h
3	88	KF-Alumina (1.0 equiv), DMF, 60 °C, 1 h
4	—	KF-Celite (1.0 equiv), MeCN, 60 °C, 12 h
5	—	KF (1.0 equiv), MeCN, 60 °C, 12 h
6	86	^{t}BuOK (1.0 equiv), MeCN, 60 °C, 1 h
7	78	NaH (1.0 equiv), DMF, 0 °C to rt, 1.5 h
8	81	NaOMe (1.0 equiv), THF, rt, 2 h

[a] Isolated yield.



R = Me, Et, Bn, allyl, 2-chloroallyl
X = I, Br

Scheme 3. α′ Functionalisation of cyclic enone **2**.

Stork and Danheiser.[26] In fact, the deprotonation at low temperature of isoindolinone **2** with the strong base LDA, followed by treatment with an appropriate alkyl halide (1.2 equiv), as shown in Scheme 3, smoothly affords a series of functionalised ketones **5a–e** and **6** at the α′-position. The results are shown in Table 2.

Reaction is quite general, allowing the recovering of the products in high isolated yields (72–90%) within 3 h in all cases. It is worth noting that if the alkylating agent is employed in excess (2.5 equiv), the major product is the α′,α′-dimethylated ketone **6** (entry 10). Appreciably, more reactive halides such as benzyl bromide (entry 12) and allyl iodide (entry 13) afford the best yields compared to primary halides, methyl and ethyl (entries 9–11). Finally, the presence of a steric hindrance in the electrophile, as shown in the case of 2-chloro-3-iodoprop-1-ene (entry 14), may be the cause of the decrease in the reaction yield. Interestingly, the introduction of olefin substituents could be employed to activate these systems towards other modifications: for example, the chlorovinyl moiety of isoindolininone **5e** may represent a starting point for the generation of α-chloroketones.[27]

Table 2
Alkylation of cyclic enone **2** with different electrophiles

Entry	α′-Substituted cyclic enone[a] (%)	Electrophiles
9	**5a** (82)	Methyl iodide (1.2 equiv)
10	**5a** (17) + **6** (61)	Methyl iodide (2.5 equiv)
11	**5b** (79)	Ethyl iodide (1.2 equiv)
12	**5c** (90)	Benzyl bromide (1.2 equiv)
13	**5d** (86)	Allyl iodide (1.2 equiv)
14	**5e** (72)	2-chloro-3-iodoprop-1-ene (1.2 equiv)

[a] Isolated yield.

In conclusion, we have described the first use of KF-Alumina as an effective base to promote HWE intramolecular reaction on a phthalimide, obtaining selectively an isoindolinone, which represents a starting structure for further modifications at α′-position of the cyclic α,β-unsaturated ketone, by choosing appropriately the electrophile agent.

Acknowledgements

This work was partly supported by a Research Project of the CAM (Comunidad Autónoma de Madrid, QO-UCM, ref. S-0505/PPQ/0344). One of the authors (V. Pace) thanks the MEC (Spanish Ministry of Education and Science) for a Ph.D. grant (MEC FPU AP2005-5112).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.029.

References and notes

1. Valencia, E.; Fajardo, V.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett.* **1985**, *26*, 993–996.
2. (a) Zhuang, Z.-P.; Kung, M.-P.; Mu, M.; Kung, J. *J. Med. Chem.* **1998**, *41*, 157–166; (b) Norman, M. H.; Minick, D. J.; Rigdon, G. C. *J. Med. Chem.* **1996**, *39*, 149–157; (c) Taylor, E. C.; Zhou, P.; Jennings, L. D.; Mao, Z.; Hu, B.; Jun, J.-G. *Tetrahedron Lett.* **1997**, *38*, 521–524.
3. Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432–1437.
4. (a) Watanabe, H.; Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 919–924; (b) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1188–1191; (c) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313–10330; (d) Couture, A.; Deniau, E.; Ionescu, D.; Grandclaudon, P. *Tetrahedron Lett.* **1998**, *39*, 2319–2320.
5. Gutiérrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem.* **1989**, *54*, 4335–4344.
6. Guillaumel, J.; Boccara, N.; Demersemann, P.; Royer, R. *J. Chem. Soc., Chem. Commun.* **1988**, 1604–1605.
7. (a) Freccero, M.; Fasani, E.; Albini, A. *J. Org. Chem.* **1993**, *58*, 1740–1745; (b) Weidner-Wells, M. A.; Oda, K.; Mazzocchi, P. H. *Tetrahedron* **1997**, *53*, 3475–3486.
8. (a) Brewster, J. H.; Fusco, A. M.; Carosino, L. E.; Corman, B. G. *J. Org. Chem.* **1963**, *28*, 498–501; (b) Milewska, M. J.; Bytner, T.; Polonski, T. *Synthesis* **1996**, 1485–1488.
9. (a) Yamamoto, I.; Tabo, Y.; Gotoh, H. *Tetrahedron Lett.* **1971**, *22*, 2295–2296; (b) Dominh, T.; Johnson, A. L.; Jones, J. E.; Senise, P. P., Jr. *J. Org. Chem.* **1977**, *42*, 4217–4221; (c) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *J. Chem. Soc., Chem. Commun.* **1985**, 1183–1184; (d) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353–355.
10. (a) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684–1687; (b) Larock, R. C.; Liu, C.-L.; Lau, H. H.; Varaprath, S. *Tetrahedron Lett.* **1984**, *25*, 4459–4462; (c) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777–4792.
11. Pierce, J. G.; Waller, D. L.; Wipf, P. *J. Org. Chem.* **2007**, *692*, 4618–4629.
12. For review, see: (a) Murphy, P. J.; Lee, S. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3049–3068. and references cited therein; (b) Hajos, G.; Nagy, I. *Curr. Org. Chem.* **2008**, *12*, 39–58. and references cited therein.
13. (a) Flitsch, W.; Peters, H. *Tetrahedron Lett.* **1969**, *10*, 1161–1164; (b) Flitsch, W.; Hampel, K.; Hohenhorst, M. *Tetrahedron Lett.* **1987**, *28*, 4395–4396; (c) Flitsch, W.; Hampel, K. *Liebigs Ann. Chem.* **1988**, 387–390; (d) Flitsch, W.; Langer, W. *Liebigs Ann. Chem.* **1988**, 391–395; (e) Flitsch, W.; Wernsmann, P. *Tetrahedron Lett.* **1981**, *22*, 719–722; (f) Flitsch, W.; Schindler, S. R. *Synthesis* **1975**, 685–700; (g) Flitsch, W.; Russkamp *Liebigs Ann. Chem.* **1983**, 521–528.
14. For a review, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. and references cited therein.
15. (a) Gouvers, J.-P.; Couthon, H.; Sturtz, G. *Eur. J. Org. Chem.* **1999**, 3489–3493; (b) Petter, R. C.; Banerjee, S.; Englard, S. *J. Org. Chem.* **1990**, *55*, 3088–3097; (c)

Dartmann, M.; Flitsch, W.; Krebs, B.; Pandl, K.; Westfechtel, A. *Liebigs Ann. Chem.* **1988**, 695–704.
16. (a) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525–2529; (b) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692–7697.
17. (a) Aitken, R. A.; Cooper, H. R.; Mehrotra, A. P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 475–483; (b) Caballero, E.; Alonso, D.; Peláez, R.; Alvarez, C.; Puebla, P.; Sanz, F.; Medarde, M.; Tomé, F. *Tetrahedron Lett.* **2004**, *45*, 1631–1634; (c) Bestmann, H. J.; Moenius, T.; Soliman, F. *Chem. Lett.* **1986**, *15*, 1527–1528.
18. See Supplementary data for detailed experimental conditions.
19. For a review, see: Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430. and references cited therein.
20. Chopard, P. A.; Clark, V. M.; Hudson, R. F.; Kirby, A. J. *Tetrahedron* **1965**, *21*, 1961–1970.
21. Pace, V.; Martínez, F.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. R. *Org. Lett.* **2007**, *9*, 2661–2664.
22. For reviews, see: (a) Blass, B. E. *Tetrahedron* **2002**, *58*, 9301–9320; (b) Basu, B.; Das, P.; Das, S. *Curr. Org. Chem.* **2008**, *12*, 141–158.
23. (a) Boullet, F. T.; Villemin, D.; Ricard, M.; Moison, H.; Foucaud, A. *Tetrahedron* **1985**, *41*, 1259–1266; (b) Hachemi, M.; Sebova, M. P.; Toma, S.; Villemin, D. *Phosphorous Sulfur Silicon Relat. Elem.* **1996**, *113*, 131–136.
24. For a review, see: (a) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401–422; (b) McKillop, A.; Young, D. W. *Synthesis* **1979**, 481–500.
25. Smith, B. S.; March, J. *March's Advanced Organic Chemistry, Reactions*, 5th ed. In *Mechanisms and Structure*; Wiley-VCH: Weinheim, 2001. p 1233.
26. Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *33*, 1775–1776.
27. Van Brunt, M. P.; Ambenge, R. O.; Weinreb, S. M. *J. Org. Chem.* **2003**, *68*, 3323–3326.