A short synthesis of conjugated unsaturated amides and esters *via* triphenylphosphine-catalysed isomerisation of acetylenic pentafluorophenyl esters†

Uli Kazmaier

Organisch-Chemisches Institut der Universität, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

Isomerisation of acetylenic pentafluorophenyl esters in the presence of phosphines gives rise to activated dienoic acids, which can be coupled directly with amines and alcohols in a simple one-pot procedure.

Highly unsaturated carboxylic and fatty acids are very common in different types of natural products.[1] Many of these sometimes very complex compounds show interesting biological activities and are applied as antibiotics.[2] Unsaturated esters are found as side-chains of sugars,[3] such as the antifungal active papulacandins,[4] or as parts of macrocyclic lactones.[5] Unsaturated amides find application as insecticides,[6] and modified peptides[7] and cyclopeptides[8] are highly interesting from a pharmaceutical point of view.

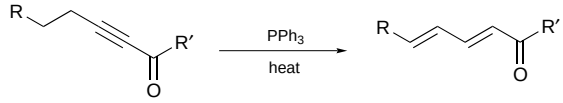
Apart from eliminations[9] and Knoevenagel condensations,[10] Wittig and Horner–Emmons[11] reactions are used frequently for the synthesis of conjugated unsaturated carboxylic acids. Besides these well established approaches, organometallic transformations, such as cross coupling reactions[12] or metal-catalysed isomerisations of acetylenes to dienes,[13] are also becoming more and more important.

Recently we described a new isomerisation of acetylenic carbonyl compounds in the presence of triphenylphosphine.[14] Similar results were obtained by Guo and Lu.[15] While acetylenic ketones can easily be isomerised in the presence of 5–10% of PPh_3 at 80–100 °C (Scheme 1), the corresponding less reactive esters react only in the presence of weak acids (*e.g.* acetic acid). If the reaction is applied to activated enynes or diynes, conjugated trienes or tetraenes can be obtained as well.[16]

The reaction probably starts with a nucleophilic addition of the phosphine on the activated triple bond, followed by a set of proton transfer steps. Perhaps these steps are accelerated by weak acids. This mechanism seams reasonable, because several of the possible intermediates could be trapped and used for further reactions, *e.g.* Michael additions.[17]

This procedure gives easy and cheap access to these interesting compounds, although problems may arise during the isomerisation process with acid- or thermo-labile compounds. Acetylenic amides only react, if at all, under even more drastic conditions,[14] which may not be 'survived' by sensitive amides, like peptides.

For an application of this process to natural product synthesis it would be desirable to work under mild conditions and/or to combine the isomerisation of an activated acetylene with a successive esterification (or amide formation), probably in a one-pot procedure. This approach can be realized by using the corresponding acetylenic pentafluorophenol esters. These relatively stable esters are used frequently in peptide syntheses, especially for the syntheses of strained cyclic peptides.[18] The isomerisation of these esters proceeds under much milder conditions (Table 1), because of the strong electron-withdrawing effect of the fluorine atoms and the resulting activation of the triple bond.



Scheme 1

Using 10 mol% of PPh_3 the isomerisation can be carried out at room temperature and under neutral conditions, which is important for the application of this procedure to sensitive substrates. Various acetylenic esters were investigated and, in general, the isomerisation was complete after stirring the reaction mixture overnight. The (*E*,*E*)-diene is formed almost exclusively (93–99%, as determined by NMR or GC analyses). If the esters tolerate higher temperatures, the amount of phosphine can be dramatically reduced, as shown with the last entries.‡ The higher temperatures are necessary for acceptable turnovers. From a synthetical point of view, it is convenient to carry out the isomerisation with 5% of phosphine at 50 °C, because under these conditions most reactions are complete after 4–5 h. The isomerisation only occurs in the presence of phosphines. No reaction was observed in the presence of tertiary amines, as determined by GC analysis, which is especially well-suited to monitoring the reaction progress. Obviously, the isomerisation proceeds directly from the acetylene to the conjugated diene. Allenic intermediates, as postulated in transition metal catalysed isomerisations,[13] could not be detected in any of the investigated examples.

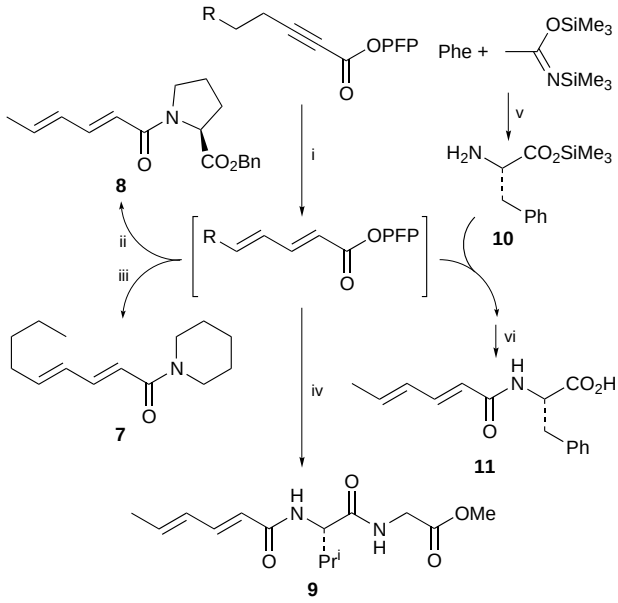
In general, the isomerisation proceeds in a very clean manner and without side reactions. Therefore the isomerised active esters can be coupled directly with nucleophiles in a one-pot procedure (Scheme 2).§ Thus conversion to the corresponding amides **7**, *e.g.* by reaction with amino acid esters **8** and peptides **9**, occurs at room temperature. To use this protocol in peptide syntheses, it would also be of interest to couple the dienoic acid to free amino acids, because the acylated amino acids obtained can be used directly for the next coupling step with further amino acids or peptides. This approach can be realized by heating the desired amino acid in toluene with bis(trimethylsilyl)acetamide (until the amino acid is completely dissolved) giving rise to the corresponding silyl ester **10**. The acylated amino acid **11** is obtained after acidic workup of the reaction mixture. The increased reactivity of the pentafluorophenol esters towards alkyl esters also allows their regioselective isomerisation and coupling, as illustrated with substrate **12** (Scheme 3).

Table 1 PPh_3-catalysed isomerisations of **5**

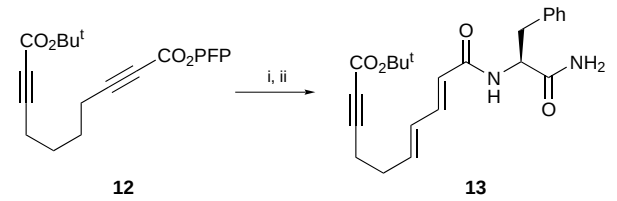
PPh_3 (%)	*T*/°C	*t*/h	Conversion (%)
10	25	2	43
10	25	14	67
10	25	14	97
5	50	4	quant.
1	50	4	46
0.1	100	40	59

The reaction is almost independent of the solvent used. Alcohols, especially sterically hindered ones, do not react under the conditions of amide formation, and they can be used as solvents for amines which are not soluble in less polar solvents. Nevertheless, esterification is possible under transesterification conditions, as described by Seebach *et al.*[19] (Scheme 4). In the presence of LiBr and 1,4-diazabicyclo[2.2.2]octane (DABCO) or DBU, acylated polyols (*e.g.* **14**) and steroids (*e.g.* **15**) can be obtained. The formation of the corresponding Weinreb amides[20] also needs higher temperatures (80 °C) in comparison to the reaction of other amines.

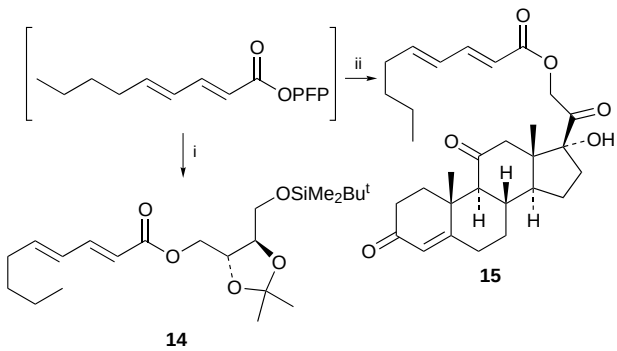
Professor Dr G. Helmchen is thanked for his generous support of this work. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.



Scheme 2 *Reagents and conditions*: i, PPh_3, toluene, 50 °C, 5 h; ii, Pro-OBn, 74%; iii, piperidine, 81%; iv, Val-Gly-OMe, 75%; v, toluene, 110 °C, 4 h; vi, H_3O^+, 63%



Scheme 3 *Reagents and conditions*: i, PPh_3 (5%), 50 °C, 5 h; ii, Phe-NH_2, room temp., 14 h, 66% over two steps



Scheme 4 *Reagents and conditions*: i, Cortison, DBU, LiBr, DMF, toluene, 80 °C, 14 h, 64%; R*OH, DBU, LiBr, toluene–THF, 80 °C, 10 h

Footnotes and References

* E-mail: ck1@ix.urz.uni-heidelberg.de

† Dedicated to Professor Huttner on the occasion of his 60th birthday.

‡ In these cases the reaction should be carried out under argon to avoid oxidation (deactivation) of the catalyst.

§ *General procedure* for the isomerisation/amide formation: 1 mmol each of alkynoic acid and pentafluorophenol were dissolved in 5 ml CH_2Cl_2 and, after addition of 0.1 mmol of DMAP, the solution was cooled to −20 °C. A solution of 1 mmol DCC in 1 ml CH_2Cl_2 was added and the mixture was allowed to warm to room temperature overnight. After filtration and evaporation of the solvent the residue was dissolved in 5 ml of toluene. After addition of 0.05 mmol of PPh_3 the solution was warmed to 50 °C for 5 h. After cooling to room temperature, 1–1.5 mmol of the corresponding amine were added and the mixture was stirred at room temperature overnight. The obtained crude product was purified by flash chromatography or crystallisation.

1 G. Habermehl and P. Hammann, *Naturstoffchemie*, Springer, Berlin, 1992.
2 U. Gräfe, *Biochemie der Antibiotika*, Spektrum, Heidelberg, 1992.
3 F. VanMiddlesworth, C. Dufrese, J. Smith and K. E. Wilson, *Tetrahedron*, 1991, **47**, 7563; Y. Doi, M. Ishibashi and J. Kobayashi, *Tetrahedron*, 1994, **50**, 8651; J. E. Hochlowski, D. N. Whittern, A. Buko, L. Alder and J. B. McAlpine, *J. Antibiot.*, 1995, **48**, 614.
4 P. Traxler, J. Gruner and J. A. L. Auden, *J. Antibiot.*, 1977, **30**, 289; A. G. M. Barrett, M. Pena and J. A. Willardsen, *J. Chem. Soc., Chem. Commun.*, 1995, 1145.
5 F. M. Arcamone, C. Bertazzoli, M. Ghione and T. G. Scotti, *Microbiol.*, 1959, **7**, 207.
6 F. Bohlmann and C. Zdero, *Chem. Ber.*, 1973, **106**, 1328.
7 A. Fredenhagen, S. Y. Tamura, P. T. M. Kenny, H. Komura, Y. Naya, K. Nakanishi, K. Nishiyama, M. Sugiura and H. Kita, *J. Am. Chem. Soc.*, 1987, **109**, 4409; J. Needham, M. T. Kelly, M. Ishige and R. J. Andersen, *J. Org. Chem.*, 1994, **59**, 2058.
8 R. Myokei, A. Sakurai, C. Chang, Y. Kodaira, N. Takahasi and S. Tamura, *Tetrahedron Lett.*, 1969, **9**, 695; M. Oka, Y.Nishiyama, S. Ohta, H. Kamei, M. Konishi, T. Miyaki, T. Oki and H. Kawaguchi, *J. Antibiot.*, 1988, **41**, 1331; H. Koshino, H. Osada, T. Yano, J. Uzawa and K. Isono, *Tetrahedron Lett.*, 1991, **32**, 7707.
9 K. Tanaka, M. Terauchi and A. Kaji, *Chem. Lett.*, 1981, 315, and references cited therein; T. Mandai, T. Moriyama, K. Tsujimoto, M. Kawada and J. Otera, *Tetrahedron Lett.*, 1986, **27**, 603.
10 J. Singh, K. L. Dhar and C. K. Atal, *Tetrahedron Lett.*, 1969, 4975.
11 D. Seebach, H. Chow, R. F. W. Jackson, K. Lawson, M. A. Sutter, S. Thaisrivongs and J. Zimmermann, *J. Am. Chem. Soc.*, 1985, **107**, 5292; U. Schmidt, A. Kleefeldt and R. Mangold, *J. Chem. Soc., Chem. Commun.*, 1992, 1687; R. W. Armstrong, *Tetrahedron Lett.*, 1994, **35**, 7743.
12 N. Lewis, P. W. McKeu and R. J. K. Taylor, *Synlett*, 1992, 898; F. Babudri, V. Fiandanese, F. Naso and A. Punzi, *Tetrahedron Lett.*, 1994, **35**, 2067; A. G. M. Barrett, M. Pena and J. A. Willardsen, *J. Chem. Soc., Chem. Commun.*, 1995, 1145.
13 B. M. Trost and T. Schmidt, *J. Am. Chem. Soc.*, 1988, **110**, 2301; D. Ma, Y. Lin, X. Lu and Y. Lu, *Tetrahedron Lett.*, 1988, **29**, 1045; D. Ma, Y. Lu and X. Lu, *J. Org. Chem.*, 1989, **54**, 1105.
14 B. M. Trost and U. Kazmaier, *J. Am. Chem. Soc.*, 1992, **114**, 7933.
15 C. Guo and X. Lu, *J. Chem. Soc., Chem. Commun.*, 1993, 394; C. Guo and X. Lu, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1921.
16 S. D. Rychnovsky and J. Kim, *J. Org. Chem.*, 1994, **59**, 2659.
17 B. M. Trost and C. Li, *J. Am. Chem. Soc.*, 1994, **116**, 10 819; C. Zhang and X. Lu, *J. Org. Chem.*, 1995, **60**, 2906; C. Zhang and X. Lu, *Synlett*, 1995, 645; K. Liou and C. Cheng, *J. Chem. Soc., Chem. Commun.*, 1995, 1603.
18 U. Schmid, A. Lieberknecht, H. Griesser and J. Talbiersky, *J. Org. Chem.*, 1982, **47**, 3261.
19 D. Seebach, A. Thaler, D. Blaser and S. Y. Koo, *Helv. Chim. Acta*, 1991, **74**, 1102.
20 S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1991, **22**, 3815.

Received in Liverpool, UK, 9th July 1997; 7/04927G