REVIEW

The Aminopropenal- and Aminopentadienal Rearrangement

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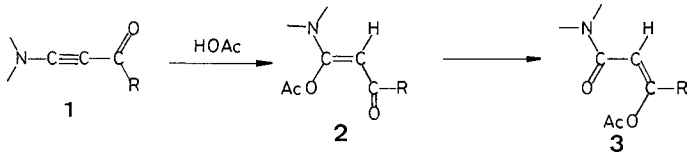
Scope and mechanism of the *aminopropenal rearrangement* are reviewed: Various 3-acyloxy-3-dialkylaminopropenals (**2**, formed by addition of acids to 'push-pull'-acetylenes **1**) rearranged quantitatively to give 3-acyloxyacrylic amides (**3**, *Schemes 1* and *22*). Since these activated enol esters reacted very selectively with amino groups of polyfunctional amino acids, 'push-pull'-acetylenes are versatile peptide reagents.

Similarly, 5-X-5-dialkylaminopentadienals (**38**, formed by addition of acids to 'push-pull'-enynes **37**) could be rearranged (*aminopentadienal rearrangement*). In this case, the rearrangement **38** → **40** → **42** (*Schemes 16* and *22*) normally stopped at the level of the quite stable 2-dialkylamino-pyrylium salts **40**. Ring opening **40** → **42** of these intermediates was quite tricky, but could be realized in several cases.

1. Introduction. – In 1966[2]) we found a simple and straightforward synthesis of 'push-pull'-acetylenes[3]) **1** [1]. This synthesis opened an access to 3-substituted 3-aminoacrylic derivatives **2** which, as dipolar olefins with an additional leaving group, were supposed to be very reactive. One of our concepts was to react the adducts **2** of AcOH or HCl with another molecule of PP-acetylene **1** to give cyclobutenes which, after elimination of the leaving group (AcO or Cl) could be converted to PP-cyclobutadienes. These first attempts[4]) failed because of a surprising rearrangement **2** → **3** of 3-acetoxy-3-dialkylaminopropenals **2** and their derivatives [2] (*Scheme 1*).

In the literature, one finds indications of similar rearrangements, which were either not recognized, or were given an incorrect mechanistic interpretation. In 1902, *Claisen*

Scheme 1



[1]) Deceased on May 7, 2015.

[2]) Published in 1968 [1].

[3]) 'Push-pull'-acetylenes will also be called 'acetylenes with electron-donating and electron-accepting groups'; in the following, 'push-pull' will be abbreviated by PP.

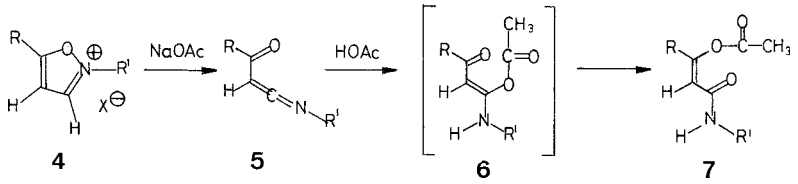
[4]) Later experiments showed that the envisaged cyclobutenes are too unstable and undergo an easy ring opening to give highly substituted PP-butadienes.

and *Mumm* [3] discovered that *N*-methyl-5-phenylisoxazolium salts **4** reacted easily with AcONa in aqueous solution. After an extensive investigation of the scope of the reaction [4–6], *Mumm* and co-workers believed that the reaction product had the structure of the imino-tautomer of **6** [6]. As *Woodward* and *Olofson* showed in 1961, isoxazolium salts **4** rearrange in the presence of carboxylates to 3-acyloxyacrylic amides **7** [7]. The reaction sequence [8] shown in *Scheme 2* has been substantiated by kinetic measurements, D-exchange, and especially by spectroscopic identification of the central intermediate, acylketene imine **5** [9]. Any direct evidence of the mechanistically plausible intermediate **6** was not available.

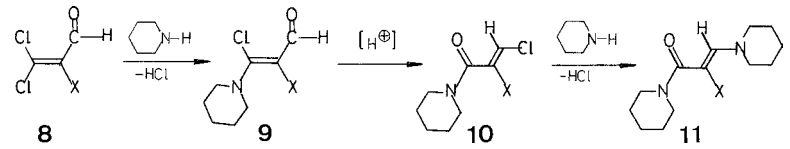
In 1958, *Kundiger* and *Morris* [10] observed that 3,3-dichloromethacrolein (**8**, X = Me) reacted with an excess of piperidine to give 3-piperidinomethacrylic piperidide (**11**). *Raulet* and *Levas* [11] were applying the sequence to 2,3,3-trichloroacrolein (**8**, X = Cl) and were proposing a quite unlikely mechanism. As we know today, the first step of these sequences is a *Michael* addition of piperidine to 2,3,3-trihaloacrolein **8**. They have to be interpreted as rearrangements of 3-halogen-substituted 3-amino-acroleins (**9** → **10**, *Scheme 3*), a reaction which had been discounted by *Raulet* and *Levas* [11] because of 'quite improbable rearrangements' ('*transpositions peu vraisemblables*').

As *Viehe* [12] demonstrated, alkyl- or aryl-substituted ynamines added acylhalides. In 1967, *Weygand et al.* [13] showed that ynamines **12** were reacting with anhydrides, too. Parallel to our studies, they observed that the hereby formed 4-acyloxy-4-dialkylaminobutenones **13** were rearranging (**13** → **14**, *Scheme 4*). Intermediates **13** of similar structure could be prepared by chloroacylation of ynamines according to *Viehe* [12] followed by reaction with carboxylates [14].

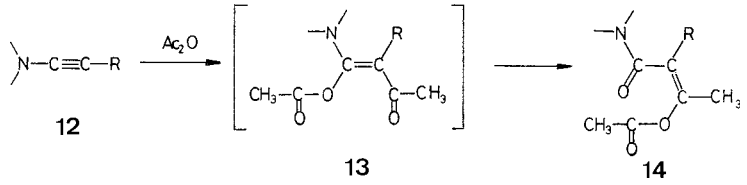
Scheme 2



Scheme 3

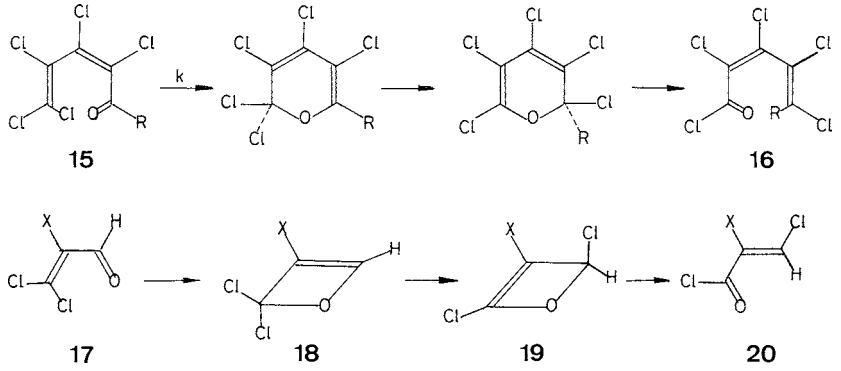


Scheme 4



Finally, we would like to mention the perchloropentadienal rearrangement, which has been discovered by *Roedig et al.* [15] in 1957, and whose scope [16], steric requirements [17], and mechanism [18] had been investigated in detail by *Roedig* and co-workers (*Scheme 5*, top). Furthermore, it is interesting to see that some highly halogenated propenals of type **17** under special conditions (high temperatures, catalysis with V_2A-catalysts or *Lewis*-acids) were rearranging to acrylic chlorides, too. For this sequence **17** → **20** (*Scheme 5,* bottom), oxetene intermediates **18** and **19** had been discussed (*Scheme 5*) [19].

Scheme 5



2. Synthesis of Push-Pull-Acetylenes. – PP-acetylenes are acetylenes with strong electron-donating, as well as strong electron-accepting groups. While dialkylamino substituents are good 'push'-groups, –*M*-substituents (like C=O, C≡N, NO_2) are good 'pull'-groups. We developed the first synthesis of PP-acetylenes with a broad scope [1][5]) [24][25]. As *Scheme 6* shows, it started with the corresponding PP-olefins **21** which already contained both PP-groups in the molecule. Bromination of the PP-olefins **21** in THF or CH_2Cl_2 quantitatively gave the so-called 'hydrobromides' which precipitated towards the end of the reaction. During addition of NEt_3, the 'hydrobromide' dissolved to give the brominated PP-olefin **22**, while $HNEt_3^+Br^-$ precipitated and was filtered off. Subsequent elimination with ^{t}BuOK gave PP-acetylenes **1** with yields around 66% (average of 13 examples, *Scheme 6*).

According to *Scheme 7*, we assume that in a first step, the PP-olefin **21** was O-brominated so that in **23** the conjugated system was fully conserved. In the rate-determining step **23** → **24**, bromine was transferred to C(2) to give **24**, whereupon the conjugative system was restored in step **24** → **25**. Both the structure of the 'hydrobromide' **25** and the configuration of the 2-bromo-PP-olefin **22** have been confirmed by ^{1}H- and ^{13}C-NMR spectroscopy (**25**: [26]) and X-ray-analysis (**22**: [27]).

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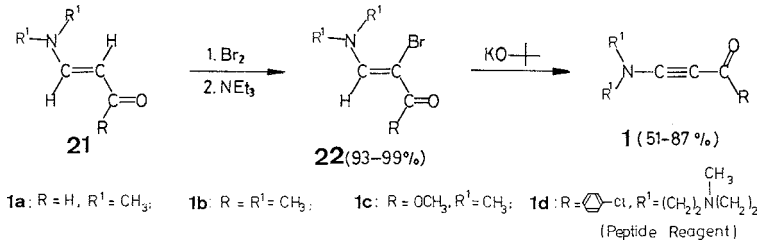
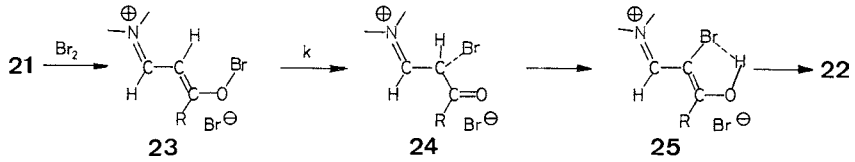
5) Other syntheses of PP-acetylenes: Acylation of stannylynamines according to *Himbert* [20] (with a broad scope); acylation of lithiumynamines according to *Kuehne* and *Sheeran* [21]; halogen-amine exchange of propargylic compounds according to *Sasaki* and *Kojima* [22]; halogen elimination from dichloroenamine carbonyls according to *Bujile* and *Viehe* [23].

Scheme 6. *Synthesis of PP-Acetylenes* **1**



Scheme 7. *Reasonable Reaction Mechanism*



3. Comments Concerning Stability and Reactivity of PP-Acetylenes. – In view of a synthetic application of a reagent, it is important that the compound is sufficiently stable. The first isolated PP-acetylenes, and especially **1a** (see *Scheme 6*), were quite sensitive towards polymerization[6]). Because of that, we tried to improve the thermal stability of PP-acetylenes [25] without reducing the reactivity towards acids. This was possible by replacing R by a *p*-substituted benzene ring (*Scheme 6*). We found that **1d** was stable at room temperature and was still easily reacting with acids. Therefore, **1d** turned out to be a very good peptide reagent [25].

Quite often, ynamine-chemists used to classify PP-acetylenes as ynamines [12][28]. This is only half of the truth, because PP-acetylenes contain the structural elements of ynamines and propargyl derivatives as well. If one compares the properties of PP-acetylenes with those of ynamines, one observes not only gradual, but general differences.

Due to the extensive π-delocalization, PP-acetylenes are less basic than ynamines. This can be important if PP-acetylenes are used for the synthesis of compounds which are prone to racemization (*e.g.* peptides). – Furthermore, the result of π-delocalization over a longer π-system is that π-charge density at C(2) of PP-acetylenes is smaller than at the β-C-atom of ynamines which results in a higher selectivity in reactions with electrophiles [28]. – In contrast to ynamines, PP-acetylenes (**1**) have an additional electron-accepting group in the molecule. This enables them to undergo *Michael* additions with nucleophiles like amines [24][29][30], while ynamines add nucleophiles only, if catalysis with *Lewis* acids takes place (which can induce rearrangements as well).

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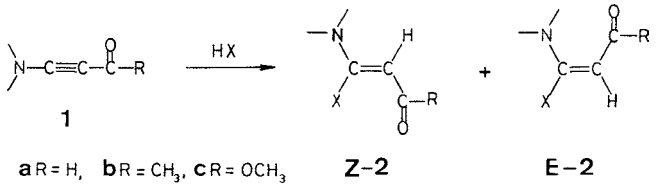
[6]) **1b** was stable for months at $-50°$; it reacted at room temperature in solution but, to our opinion, it was not stable enough for serving as a routine peptide reagent.

4. Addition of Acids to PP-Acetylenes. – PP-acetylenes (**1**) reacted easily and with high yields (of 80–90%) with inorganic acids like HF, HCl, HBr, and with phenol[7]) to give 3-X-3-dialkylaminoacrylic compounds (*Scheme 8* [31]). For preparative purposes, the addition of carboxylic acids was much more important: It was close to quantitative, but the primary adducts **2** were normally not observed even at $-60°$ due to an easy rearrangement to give 3-acyloxyacrylic amides (*Scheme 1*). It is important to note that carboxylic acids bearing additional functional groups (like OH, NH_2 or SH) can easily be added without side reactions [32]. Obviously, the addition of carboxyl groups to PP-acetylenes is much faster than *Michael* addition of amines, thiols, or alcohols.

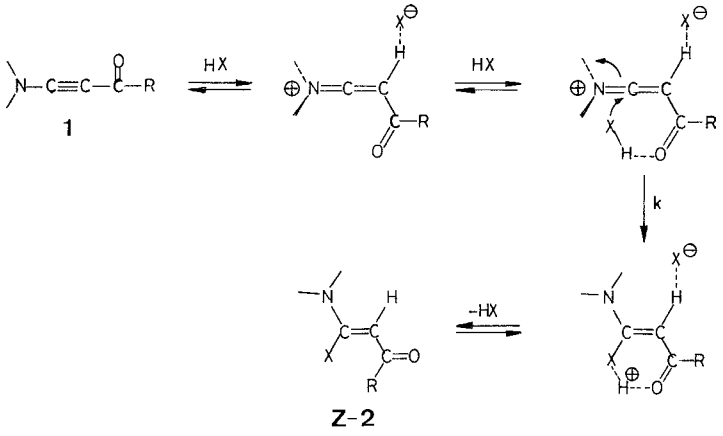
The steric course of the addition of acids depended on the rest R of the carbonyl group: Starting with 3-(dimethylamino)prop-2-ynal (**1a**) and 4-(dimethylamino)but-3-yn-2-one (**1b**), one observes stereoselectively the *trans*-addition, while starting with methyl 3-(dimethylamino)prop-2-ynoate (**1c**) the *trans*-adducts (*Z*)-**2** and *cis*-adducts (*E*)-**2** were formed in similar amounts [31].

Kinetic investigations [31] showed that the addition of phenol to **1a** was of a third-order reaction: It was second-order with respect to phenol and first order with respect to the acetylene **1a**. Furthermore, the rate of addition slowed down with increasing solvent polarity. These results were in agreement with the mechanism formulated in *Scheme 9*, where the rate-determining step consisted in the addition of a second

Scheme 8



Scheme 9



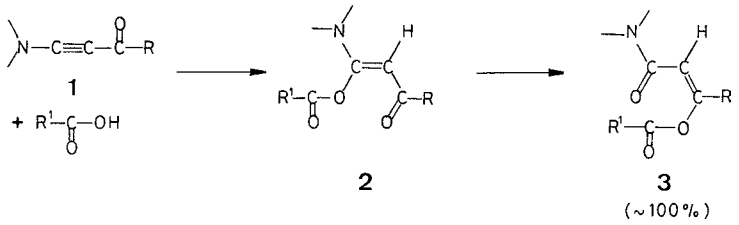
7) Kinetic experiments showed that phenol behaved as an acid, but it reacted slower with PP-acetylenes than HCl.

molecule of acid to the protonated PP-acetylene. Under the chosen aprotic conditions, the second molecule of acid was supposed to form a hydrogen bond with the carbonyl group which strongly increased the chances for the observed *trans*-addition.

5. The Aminopropenal Rearrangement: Rearrangement of the Adducts of Carboxylic Acids to PP-Acetylenes. – 5.1. *Preparative Results.* According to *Chapter 4*, the addition of carboxylic acids was expected to give, for R = H and R = alkyl, stereoselectively the *trans*-adducts **2**. Instead of that, with nearly quantitative yields, (*Z*)-3-acyloxyacrylic amides (**3**, R = H) and crotonic amides (**3**, R = Me) were isolated[8]). This remarkable rearrangement took place very easily and stereospecifically even at $-50°$. The reaction proceeded at low temperatures as a simple 'one-pot reaction'. Due to the high yields, isolated products didn't have to be purified in most cases. The rearrangement worked with all ynamine aldehydes **1a** and ynamine ketones **1b** investigated [34]. Exceptions were ynamine esters **1c** or ynamine amides. Although they added acids with high yields [31], the addition products did not rearrange.

Enol esters **3** were prepared nearly quantitatively from simple carboxylic acids [34]. It was interesting to see that polyfunctional carboxylic acids reacted very selectively with PP-acetylenes according to *Scheme 10* [32]. Hydroxycarboxylic acids (with primary, secondary, tertiary, and phenolic OH groups) as well as amino- and sulfanylcarboxylic acids reacted at $-50°$ fast and quantitatively. This was not trivial, since amines, alcohols, as well as phenols could undergo *Michael* additions with PP-acetylenes, too [29]. Obviously in case of concurring COOH, OH, NH_2, and SH groups, the addition of carboxylic acids was much faster.

Scheme 10. *The Aminopropenal Rearrangement* **2** → **3** (X = AcO)



Generally, the enol esters **3** were stable at room temperature and they were not very sensitive towards hydrolysis. Exceptions were enol esters formed by addition of formic acid and trifluoroacetic acid, which decomposed at room temperature. For example, the enol esters **3a** and **3b** obtained by addition of formic acid to PP-acetylenes **1a** and **1b**, were splitting off carbon monoxide in a definite way [34].

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[8]) An early German version of the 'Aminopropenal Rearrangement' (with emphasis on peptide synthesis and including additional tables of the preparative results) has been published in 1973 with tables of the preparative scope of the rearrangement [33]. Average yield: 97% (9 examples, variation of **1** [34] [35]); 96% (10 examples, varying the carboxylic acid [34]); 95% (18 examples, varying polyfunctional carboxylic acids [32]).

5.2. *Mechanism of the Rearrangement* **2** → **3** (*Scheme 10*) [36]. With respect to the mechanism of the aminopropenal rearrangement, the following preparative results are important:

HF, HCl, HBr, and phenols (which kinetically behave like acids) react with PP-acetylenes **1a** and **1b** with high yields and a high stereoselectivity to give the *trans*-addition products **2**. If carboxylic acids (whose adducts **2** normally can't be observed even at $-50°$ by NMR) behave similarly, then the added carboxylic group is supposed to sit in *cis*-position of the carbonyl group.

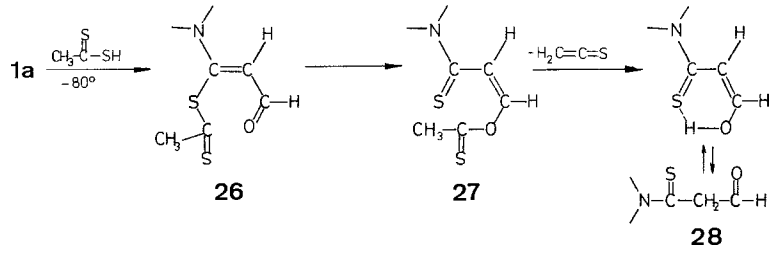
The steric course of the rearrangement is remarkable: Under kinetic control, one exclusively observes the (*Z*)-configured enol esters **3**.

The rearrangement proceeds even if small amounts of carboxylic acid are reacted with an excess of PP-acetylene at $-50°$.

These results hinted at an intramolecular acylation **2** → **3** of the carbonyl group of the intermediate **2**. Since kinetic measurements were impossible because of the instability of the intermediates **2**, we were reacting ethane(dithioic) acid with 3-(dimethylamino)prop-2-ynal (**1a**) and analyzed the distribution of sulfur in the rearranged product **27**.

The reaction of 3-(dimethylamino)prop-2-ynal (**1a**) with ethane(dithioic) acid demonstrated that the distribution of sulfur in the reaction products was in agreement with an intramolecular shift of the thioacetyl group (**26** → **27**; *Scheme 11*), although the sequence was more complicated than expected. After a short reaction time at $-80°$, the ^{1}H-NMR spectrum showed the clean signals of the *Michael* adduct **26** besides the (*Z*)-enol ester **27**[9]), which equilibrated at $-40°$ with the (*E*)-isomer **27**. At $-20°$ elimination of thioketene began, and after 1 h at 20° the clean spectrum of the keto–enol equilibrium of **28** was recorded.

Scheme 11. *Reaction of* **1a** (R = H) *with Ethane(dithioic) Acid* [36]



6. Rearrangement of the Adducts of Hydrogen Halides[10])**.** – The addition products of HCl and HBr with PP-acetylenes could be rearranged (*Scheme 12*), but, in contrast to the adducts of carboxylic acids, the reaction **2** → **3** had to be catalyzed by acids or *Lewis* acids, and the stereoselectivity observed for the adducts **2** (X = R′–COO) was lost. Since the yields were only good for the HCl-adducts, the scope of the reaction was very limited.

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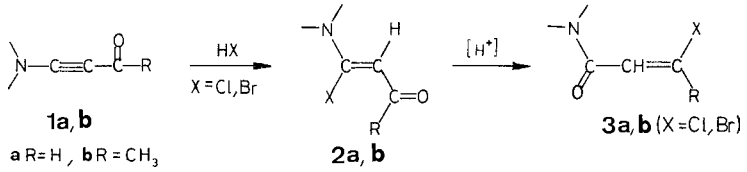
[9]) This is one of the rare cases where the primary adduct **26** was observed!

[10]) No rearrangement has been observed for the HF-addition products **2** (X = F).

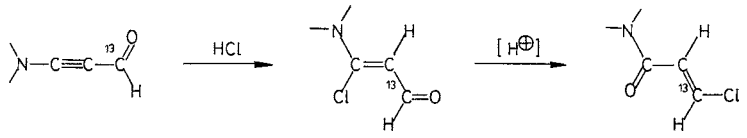
Scheme 12[11])



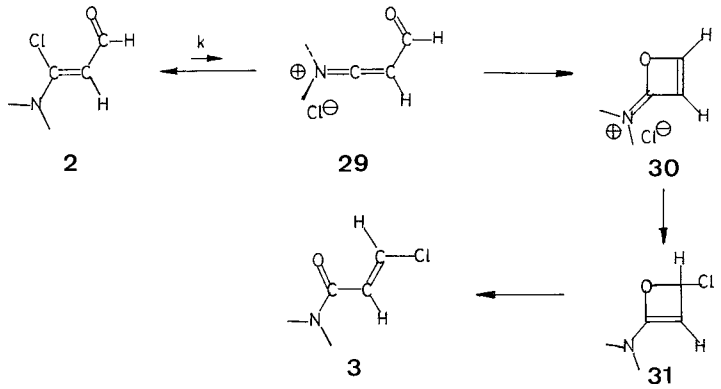
What was interesting however were the mechanistic aspects, because the mechanism which has been shown to be valid for the rearrangement of the addition products of carboxylic acids **2** (X = R′COO) was not working for HCl-adducts **2** (X = Cl), because rearrangements proceeding over 6-membered rings are not possible!

Kinetic investigations showed that the rearrangement of **2a** (X = Cl) → **3a** (X = Cl) was indeed catalyzed by acids. The reaction was *pseudo*-first order in **2a**, and the reaction rate strongly increased with increasing solvent polarity [36]. Labelling experiments convincingly showed that the carbonyl-C-atom of the starting material **2** was shifted to position 3 or the product **3** during rearrangement [37] (*Scheme 13* and *Figure*). All the results support the mechanism given in *Scheme 14* [36].

Scheme 13



Scheme 14. *Proposed Rearrangement Mechanism for* **2a** (X = Cl)



We assumed that the rate-determining step was the removal of chloride from **2**, which was catalyzed by traces of acid. The hereby formed vinyl cation **29** was transformed into the strained, but electronically stabilized 2*H*-oxet-2-iminium **30**[12]).

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[11]) From a preparative point of view, only the HCl-adducts were interesting (**3a**, X = Cl: 80%; **3b**, X = Cl: 68%). The rearrangement of HBr-adducts proceeded easily, but with low yields (**3a**, X = Br: 20%; **3b**, X = Br: 15%).

[12]) The first to propose an oxetene intermediate was Prof. *K. Hafner* during discussions in Darmstadt (*ca.* 1967).

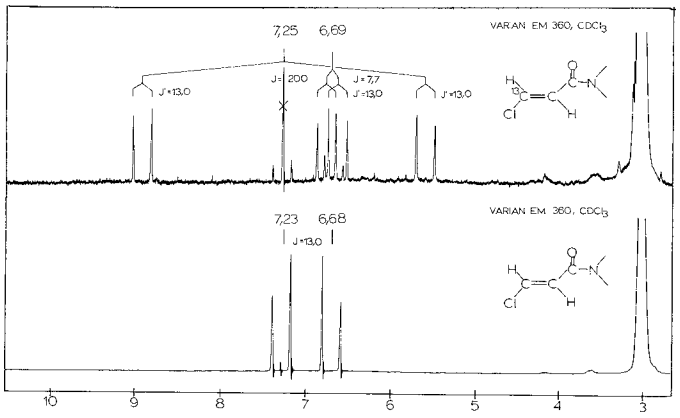


Figure. *[1]H-NMR-spectra of the reaction product of [13]C(1)-labelled* **2a**[13]) (X = Cl) *to give* **3a** (top) *as well as of not labelled* **3a** (X = Cl, bottom)

After re-entrance of chloride (**30** → **31**) and ring opening, 3-chloroacrylic amide **3** (X = Cl) was formed. – That meant that in the course of the rearrangement Cl and O exchanged their places, while the catalyst facilitated the removal of chloride (**2** → **29**).

The *Figure* shows that during rearrangement of 3-chloro-3-(dimethylamino)prop-2-enal (**2a**, X = Cl), the ^{13}C-label was shifted from C(1) to C(3) of 3-chloroacrylic amide **3a** (X = Cl): After the rearrangement, H–C(3) of **3a** showed an additional large ^{1}J(C,H)-coupling of 200 Hz, while H–C(2) was split by an additional ^{2}J(C,H)-coupling into a *doublet* of *doublet*s. The signals of 15% of unlabeled **3a** were visible, too.

7. Application of the Rearrangement: **Push-Pull-Acetylenes for Peptide Synthesis.** – 7.1. *General Remarks.* According to *Scheme 10*, reaction of various simple and even polyfunctional carboxylic acids with PP-acetylenes (**1**) gave stereoselectively activated enol esters **3** in nearly quantitative yields [31][32][34].

Since the 1960's activated esters have become very important with respect to peptide synthesis [38]. Enolesters of type **7** (*Scheme 2*) played a key role in the peptide synthesis *via* isoxazolium salts, which has been developed by *Woodward*, *Olofson*, and *Mayer* [39] and was optimized later by *Woodman* [40]. The method had a considerable scope and was characterized by mild reaction conditions and low racemization. However, minor side reactions could not be avoided, which were mainly caused by the secondary amino group of **6**, as well as by the acylketeneimine intermediate **5** (*Scheme 2*) [41].

Ynamines have been tested as peptide reagents by *Buijle* and *Viehe* [42], *Weygand et al.* [43], and *Steglich et al.* [14][44]. Reaction of acetic anhydride with ynamines **12**, as depicted in *Scheme 4*, gave activated enol esters **14** [14]. Due to their high reactivity, ynamines have shown to be very versatile reagents, especially in dehydration reactions [12]. However, as we pointed out before, ynamines **12** were very often not very

[13]) ^{13}C-content of C(1) of **2a**: 85%.

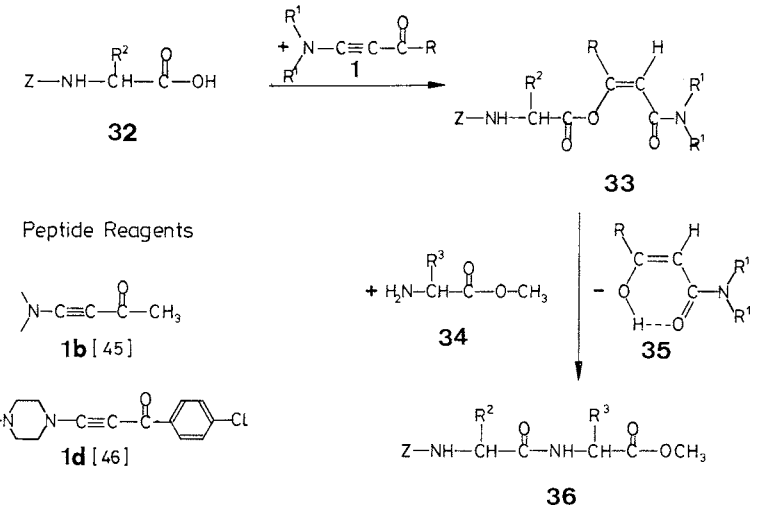
selective, and this showed up in their applications to peptide synthesis, as far as racemization was concerned. According to *Weygand*, racemization with ynamines was even higher than with dicyclohexylcarbodiimide [43].

Compared with isoxazolium salts **4** [39][40][41] and ynamines **12** [12][14], PP-acetylenes **1** could offer several advantages as peptide reagents: Compared with ynamines, their characteristics are a lower basicity, as well as a higher selectivity. Compared with isoxazolium salts, enol esters **3** have a tertiary amide function, so that some side reactions (typical for isoxazolium salts) cannot occur.

7.2. *PP-Acetylenes for Peptide Synthesis*[14]). 4-(Dimethylamino)but-3-yn-2-one (**1b**) was prepared by bromination/elimination of the corresponding PP-olefin [1][24], and there was no doubt on its outstanding peptide reagent [45] ability, but it was not very stable at room temperature[6]); that's why we were synthesizing thermally more stable PP-acetylenes such as **1d** for peptide synthesis [46]. First experiments showed that carboxylic amides could easily be prepared in a simple 'one-pot reaction' by adding carboxylic acids to the new PP-acetylenes in a first step, followed by adding the amine to the same solution in a second step [35].

For peptide synthesis, we used the thermally stable, crystalline 1-(4-chlorophenyl)-3-(4-methylpiperazin-1-yl)prop-2-yn-1-one (**1d**). Normally, the reaction time for a 100% conversion of the carboxylic component **32** with **1d** at 20° in CH_2Cl_2 was *ca.* 2 h, while the reaction of the enol ester **33** with the amine component **34** to give the peptide **36** took *ca.* 12 h[15]). The by-product **35** was easily separated. To observe the complete linking of two sterically hindered amino acids, polarimetry was recommended.

Scheme 15. *Peptide Syntheses with PP-Acetylenes* [45][46]



[14]) For an extensive survey, see [33].

[15]) This could be a limiting factor for linking long peptide chains. It was clear that reaction times of the PP-acetylene **1b** would be considerably shorter.

So far, PP-acetylenes **1b** [45] and **1d** [47] have been very useful in peptide synthesis:

- A series of Z-protected amino acids **32** have been linked to esters of amino acids **34** (9 examples, average yield: 'crude': 96%[16]); pure: 84%) [47].
- Furthermore, Z-protected amino acids have been successfully linked to esters of polyfunctional amino acids (7 examples, average yield: 'crude': 95%[14]), pure: 84%) [47].
- And finally, Z- and Boc-protected amino acids with polyfunctional carboxy components have been linked to esters of simple amino acids (9 examples, average yield 94%) [45].

These results showed that PP-acetylenes **1b** and **1d** were very versatile peptide reagents: Compared to ynamines **12** [42][43], they reacted much more selectively and did not induce racemization. Some side reactions reported for ynamines did not occur. Compared to isoxazolium salts **4** [40][41], they had a tertiary amino group and could not undergo some side reactions typical for isoxazolium salts.

8. The Aminopentadienal Rearrangement. – 3-(Dimethylamino)prop-2-ynal (**1a**, R = H) (as well as the corresponding ketone **1b** (R = Me)) reacted easily with carboxylic acids and HCl, and the hereby formed 3-X-3-(dimethylamino)prop-2-enal **2a** nearly quantitatively rearranges to give 3-chloro- (X = Cl) and 3-acyloxyacrylic amides **3** (X = AcO) (see *Schemes 10* and *12*). As formulated in *Scheme 14*, the addition products **2** of HCl rearranged by a mechanism which includes 2*H*-oxet-2-iminium **30** as intermediates. In a similar way (compared with PP-acetylenes **1**), PP-enynes of type **37** should add acids (**37** + HX → **38**), and the hereby formed 5-X-5-dialkylaminopentadienals **38** could rearrange after acid-catalyzed removal of X^- (**38** → **39**), ring closure to aminopyranium salts **40**, re-entrance of X^- (**40** → **41**), and ring opening (**41** → **42**). In this vinylogous rearrangement the aminopyranium salts **40** would correspond to the 2*H*-oxet-2-iminium salts **30** of *Scheme 14*.

8.1. *Synthesis of PP-Enynes* **37***; Addition of Acids* (**37** + HX → **38**). For a long time, an investigation of this attractive rearrangement was not possible, because before 1990 only two highly substituted PP-enynes of the type **37** were known [48][49]. Parallel to our work [50], three PP-enynes have been synthesized in 1990 (*Scheme 16*) [51][17]).

PP-enynes were available in good yields (around 60%) by Pd(0)-catalyzed coupling of 2-(trimethylsilyl)ethynamines **43** [52][53] with 3-iodoprop-2-enal (**44a**) and 4-iodobut-3-en-2-one (**44b**) [54][18]). They added easily a variety of carboxylic acids as well as hydrogen halides HF, HCl, HBr, and HI [55] in a stereospecific way to give the *trans*-addition products which were identified by NMR-spectroscopy and could be

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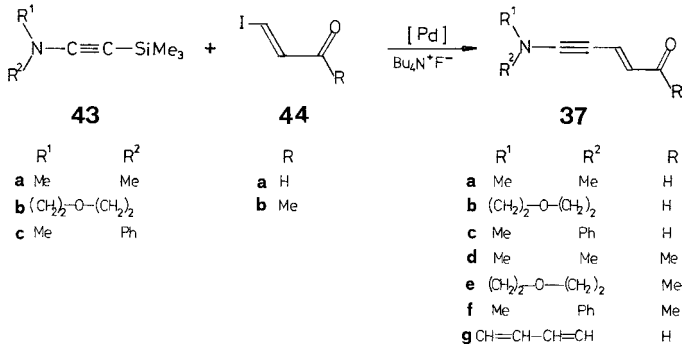
16) Melting points of 'crude products' were only 2–3° below melting points of pure products.

17) Three PP-enynes have been synthesized in a surprisingly simple way by aldol-condensation of PP-acetylenes with ketones [51]. Compared to that synthesis, our Pd(0)-catalyzed coupling of trimethylstannyl- as well as of trimethylsilylynamines (*Scheme 16*) has a much larger scope and allows the synthesis of several 5-(alkylamino)pent-2-en-4-yne-als **37** (R = H).

18) Similar yields are obtained in couplings with (tributylstannyl)ethynamines [54], but purification was not so easy.

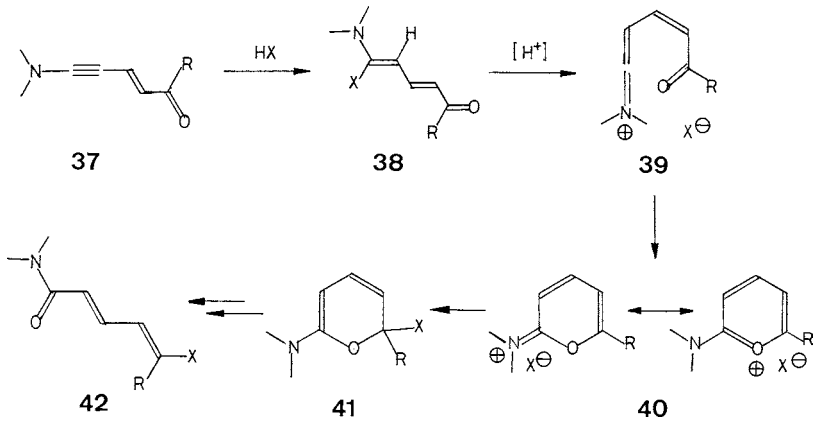
Scheme 16



isolated in most cases for X = AcO, F, and Cl [55][56][19]). Qualitatively, the rate of addition **37** + HX → **38** increased with increasing strength of the acid. For example, HF as well as AcOH added noticeably slower than HCl, HBr, and HI, while uncatalyzed additions of phenol were very slow [57][20]).

8.2. *Cyclization to Pyranium Salts* **40**. First attempts to realize the 'aminopentadienal rearrangement' showed a surprising result in so far, that the adducts **38** rearranged in the presence of traces of acids, but did not give the expected rearrangement products **42** (*Scheme 17*): The rearrangement ended at the level of the 2-aminopyranium salts **40**[21])! Qualitatively, the rate of the reaction **38** → **40** increased with increasing leaving quality of X. So, 5-X-5-aminopentadienals **38** with

Scheme 17. *The Aminopentadienal Rearrangement*



[19]) Mechanistically, one would expect (*Z*)/(*E*)-mixtures, but due to the approach of bond lengths in PP-dienes, the (*Z*)/(*E*)-equilibrium shifted to the side of the sterically favorable (*Z*)-isomer with an all-*trans*-arrangement of the N–C = C–C = C–C = O skeleton (see **38** in *Scheme 17*).

[20]) 50% Conversion after up to two weeks!

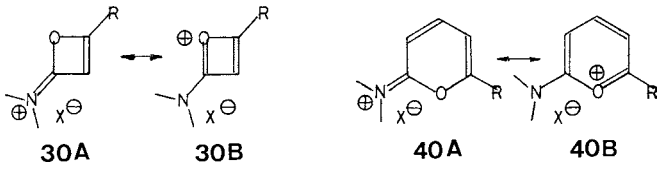
[21]) 14 examples, average yield 73%; X = F, Cl, Br, I, AcO, PhO, BF_4; for R, R^1, R^2 see *Scheme 16* [56].

good leaving groups were rearranging so fast that it was not easy to isolate the adducts **38**. That was why PP-enynes **37** could easily be reacted with 1.05 mol-equivalents of HCl, HBr, or HI to 2-aminopyranium salts **40** in a simple 'one-pot-reaction' [56]. On the other hand, adducts **38** with comparably poor leaving groups (X = F, AcO) were only rearranging in the presence of an excess of acid. These observations hinted at the fact that the rate-determining step of the conversion **38** → **40** was the (acid-catalyzed) removal of X (**38** → **39**).

2-Aminopyranium halides **40** (X = F, Cl, Br, I) were quite unreactive and did not rearrange spontaneously to 5-halopenta-2,4-dienamides **42**. In that respect, there was a big difference between 5-amino-5-chloropenta-2,4-dienal (**38a**, X = Cl) and 3-amino-3-chloroprop-2-enal (**2a**, X = Cl, *Scheme 12*), which easily rearranged at 0° in the presence of traces of acid to give 3-chloroacrylic amides (**3a**, X = Cl) [2][24]. There, according to mechanistic investigations [36], 2*H*-oxet-2-iminium salts **30** were the intermediates.

We believe that the reason for the different behavior of 3-amino-3-chloroprop-2-enals **2** and of 5-amino-5-chloropenta-2,4-dienals **38** was based on the different energies of the intermediates **30** and **40** (*Scheme 18*). 2*H*-Oxet-2-iminium salts **30** are highly strained compounds without resonance stabilization (because the energy of **30A** would be increased by the contribution of the 'antiaromatic' structure **30B**). On the other hand, 2-aminopyranium salts **40** are basically strain-free molecules whose energy is lowered by π-delocalization (see **40B**). This reasonably explained why 2-aminopyranium salts without nucleophilic counterions X^- were not prone to an easy ring opening of the type **40** → **42**. Despite of that, there were possibilities to favor a ring opening of the pyranium salts and to realize the envisaged 'aminopentadienal rearrangement' **38** → **40** → **42**.

Scheme 18

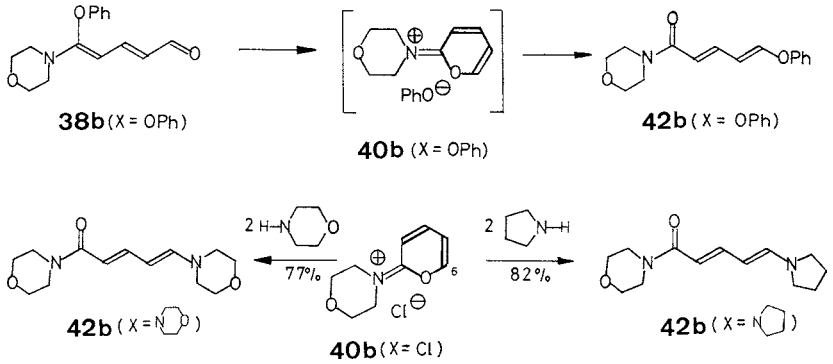


8.3. *Realization of the Pyranium Salt Ring Opening* (**40** → **42**). A rather theoretical possibility consisted in the synthesis of pyranium salts with nucleophilic counterions. This was kind of a 'balancing act' because addition of HX to the PP-enyne **37** was slowed down (due to the lowered acidity of HX). The reaction of phenol with 5-(morpholin-4-yl)pent-2-en-4-ynal (**37b**) was such a borderline case which proceeded very slowly (26 days at 20°!), but produced 5-phenoxypenta-2,4-dien-1-one **42b** (X = PhO) in a yield of 66% [57] (*Scheme 19*, top).

Since many aminopyranium chlorides and -acetates **40** were nearly quantitatively available, one could directly react them with amines (*Scheme 19*, bottom).

It would be elegant to apply an 'assisting nucleophile' for inducing the ring opening, which could then be replaced (through an addition-elimination mechanism) by the original counterion. This worked in some cases, but the yields were rather low. For

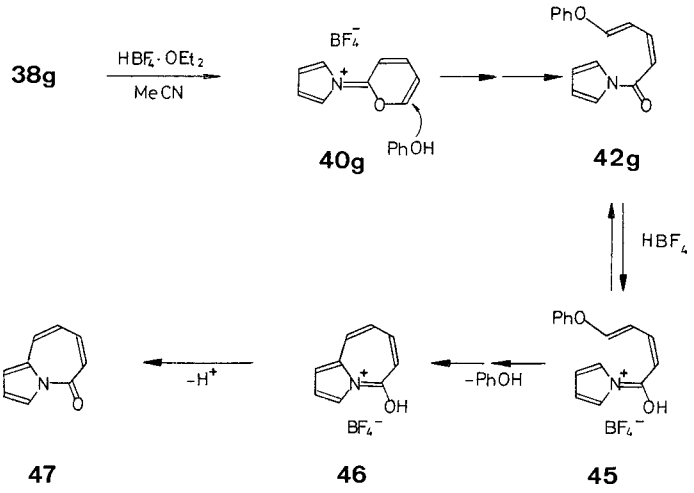
Scheme 19



instance, reacting **40b** (X = AcO) (which by itself shows no tendency towards ring opening) in the presence of NEt_3 gave **42b** (X = AcO) in moderate yields [57].

Finally, there was the possibility to replace the dialkylamino group of the PP-dienal **38** by a weaker π-donor, with the intention to raise the energy of the 2-aminopyranium salt **40** and to make it more reactive. In fact, this worked with 5-phenoxy-5-(1*H*-pyrrol-1yl)-penta-2,4-dienal (**38g**) [57] (X = OPh), but after treatment of **38g** with HBF_4, the color of the solution turned to deep red due to formation of 5-hydroxypyrrolo[1,2-*a*]azepinium tetrafluoroborate (**46**) (*Scheme 20*): Obviously the ring opening **40g** → **42g** was working, but the ring opening product **42g** was cyclizing to give the known [58] 5*H*-pyrrolo[1,2-*a*]azepin-5-one (**47**) [57].

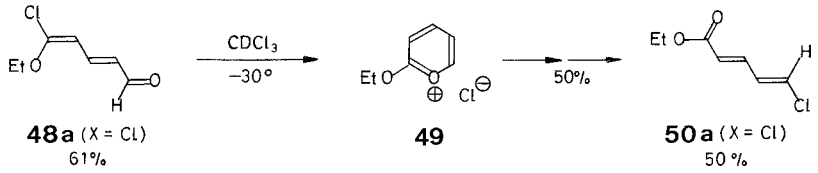
Scheme 20



These results show that the 'Aminopentadienal rearrangement' works under appropriate conditions!

8.4. *Rearrangement of PP-Dienes with Alkoxy and Phenoxy Substituents.* As *Scheme 21* demonstrates, the dialkylamino substituent of the PP-diene **38** may even be replaced by the ethoxy group [59][60]. 5-Chloro-5-ethoxypenta-2,4-dienal (**48a**) (X = Cl)[22]) slowly reacted in $CDCl_3$ (traces of acid!) to give the (*E*)/(*Z*)-mixture of the ethyl 5-chloropenta-2,4-dienoate (**50a**; *Scheme 21*). The same reaction occured with 5-chloro-5-phenoxypenta-2,4-dienal. Very surprisingly however, the corresponding methylthio- and phenylthio-derivatives behaved very differently from **48a** [60][61].

Scheme 21[23])[24])



48a (X = Cl) 61% **49** **50a** (X = Cl) 50 %

9. Summary. – PP-acetylenes **1** reacted quantitatively with carboxylic acids to give 3-acycloxyacrylic amides **3** (R = H) and crotonic amides **3** (R = Me). Normally the primary addition products **2** (X = AcO) could not be observed due to a fast intramolecular shift of the acyl group ('**aminopropenal rearrangement**'). Since PP-acetylenes selectively reacted with carboxy groups and the hereby formed enol esters **3** selectively reacted with amino groups, PP-acetylenes are proofed to be good peptide reagents (*Scheme 22*).

HCl and HBr reacted with PP-acetylenes **1** as well, but for the rearrangement of the adducts **2** → **3** (X = Cl, Br) there must be another rearrangement mechanism. According to kinetic investigations and labelling experiments the reaction proceeded over 2*H*-oxet-2-iminium salts **30**.

For investigating the so far unknown '**aminopentadienal rearrangement**', a new synthesis of PP-enines **37** was found, and the addition of various acids to PP-enynes **37** + HX → **38** was investigated. Most addition products **38** of acids (X = F, Cl, Br, I, AcO, PhO) could be rearranged to the quite unreactive 2-aminopyranium salts **40**. The envisaged ring opening **40** → **42** was quite tricky, but could be accomplished in several cases.

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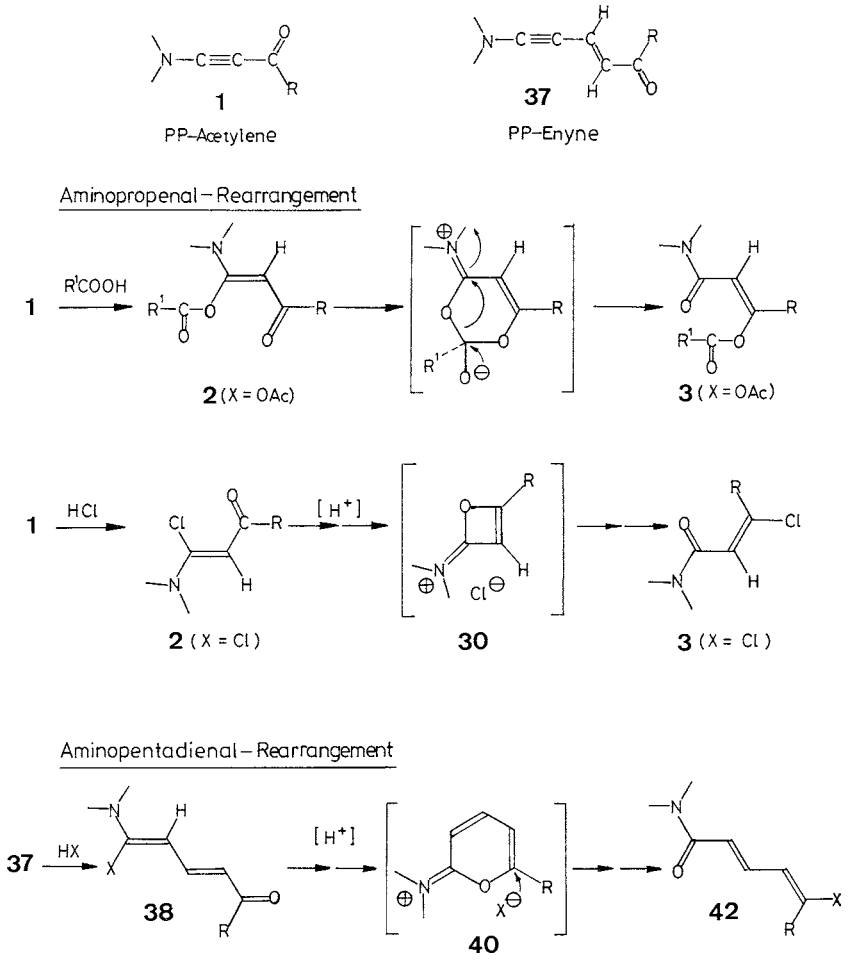
[22]) HCl-addition to 5-ethoxypent-2-en-4-ynal gave stereoselectively the *cis*-adduct!

[23]) For the synthesis of PP-enynes with EtO-, PhO-, MeS- and PhS-groups as π-donors see [60].

[24]) Crude yield of **50a** (X = Cl) according to NMR: 75%.

Scheme 22



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