Tetrahedron Vol. 41, No. 19, pp. 4057 to 4078, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

CONVENIENT APPROACHES TO HETEROCYCLES VIA COPPER-CATALYSED ADDITIONS OF ORGANIC POLYHALIDES TO ACTIVATED OLEFINS[1]

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(*Received in Germany* 28 *June* 1985)

Abstract. - An efficient method for the synthesis of 2,3-dichloro-5-substituted (Cl, CF_3, alkyl) pyridines 29 starting from the 1:1 adducts of the copper-catalysed addition of chloral or the corresponding 2,2-dichloroaldehydes to acrylonitrile is presented. Proper choice of experimental conditions allows the preparation of 29 in a one-pot process. Similarly, the CuCl-catalysed reaction of methyl itaconate with several trichloromethyl compounds R-CCl_3 gives 6-R-substituted 2-pyrone derivatives 40 via dehalogenation and subsequent thermal ring closure of the primary 1:1-adducts. The new electrophilic 2-pyrone 40b undergoes [4+2]-cycloaddition reactions with inverse electron demand with a number of olefins and acetylenes, allowing thereby regioselective transfer of a trifluoromethyl group from a simple Freon derivative (1,1,1-trichloro-2,2,2-trifluoroethane) into more complex organic molecules. Finally, the 1:1-adduct of trichloroacetylchloride with methyl acrylate allows a very convenient synthesis of novel N-substituted derivatives 66 of pyroglutamic acid as well as of proline.

INTRODUCTION

Copper and its compounds are outstanding in the transition element series for the variety and usefulness of their applications in organic synthesis. Although the general Cu-catalysed reaction between an olefin or a conjugated diene and an organic polyhalide to form a 1:1-adduct was formulated as early as 1963,[3] it would seem to us that organic chemists have not yet fully appreciated the preparative importance of this fundamental reaction. This is mainly due to the fact that traditionally either organometallic or telomeric aspects of the reaction were explored, but rarely the adducts as intermediates or as target molecules in their own right. Moreover, many interesting results remain hidden in the patent literature.

The structures of the organocopper species involved in the reaction and the mechanisms by which they react are still only vaguely understood. Originally, Asscher and Vofsi[3,4] proposed a redox-transfer chain mechanism: the catalyst (e.g. Cu(I)Cl) is supposed to participate in the chain propagation as a chlorine atom transfer agent, which in its oxidised form is a much more reactive chlorine donor than the organic polyhalide (eqs. 1-3).

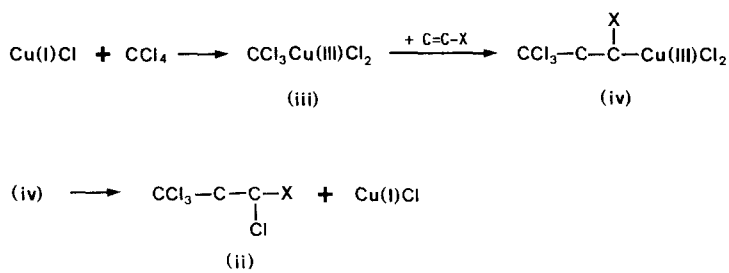
$$Cu(I)Cl + CCl_4 \longrightarrow Cu(II)Cl_2 + \bullet CCl_3 \qquad (1)$$

$$\bullet CCl_3 + C{=}C{-}X \longrightarrow CCl_3{-}C{-}\overset{\bullet}{C}{-}X \qquad (2)$$

$$CCl_3{-}C{-}\overset{\bullet}{C}{-}X + Cu(II)Cl_2 \longrightarrow CCl_3{-}C(Cl){-}C{-}X + Cu(I)Cl \qquad (3)$$

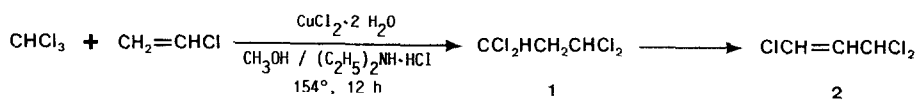
(i) (ii)

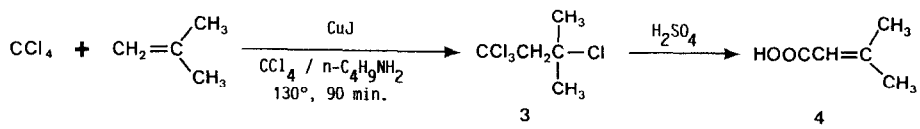
A number of facts, however, indicate that neither $\bullet CCl_3$ nor radical (i) enter the bulk of the solution. If this were the case, a considerable amount of telomer formation would be expected with highly reactive olefins such as styrene, alkyl acrylates and acrylonitrile, even of high organic polyhalide/olefin ratios.[5] However, the exclusive formation of 1:1-adducts of type (ii) is a prominent feature of this copper-catalysed reaction.[6] Furthermore, the distribution and type of products obtained under free-radical initiation conditions, e.g. in the presence of benzoyl peroxide, are different from those obtained with Cu-catalysts.[3b,5b,7] The above cited facts indicate that the free radicals formed by the reaction of organic polyhalides with copper salts are different from "normal" free radicals such as $\bullet CCl_3$ and (i), due to coordination or interaction with the metallic species. However, it remains to be demonstrated whether CuCl cleaves the carbon-halogen bond homolytically to generate a carbon radical and Cu(II)-species (eq. 1) or by a process of oxidative addition to generate a Cu(III)-species (iii) (eq. 4),[8] followed by insertion of the olefin into the carbon-copper(III) σ-bond of (iii) and halogen ligand transfer (reductive elimination) within the new Cu(III)-species (iv) thus formed.



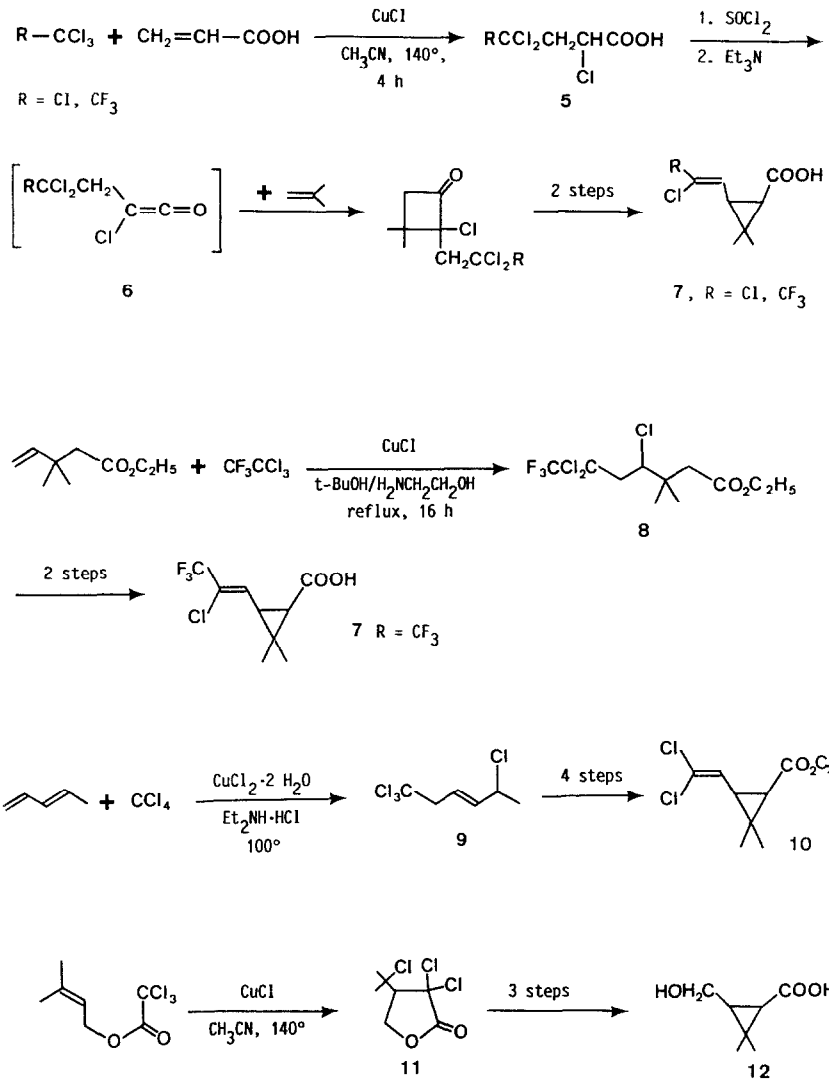
(4)

Notwithstanding this mechanistic uncertainty, the reaction between many kinds of terminally unsubstituted olefins and conjugated dienes and a variety of organic polyhalides can be accomplished very easily. Typically, heating both components in 1:1 to 1:3 ratios in acetonitrile in the presence of 1-10 mol % of Cu(I) or Cu(II) salts, preferably CuCl, affords 1:1-adducts in good to excellent yields.[3a,6b,6c,9]



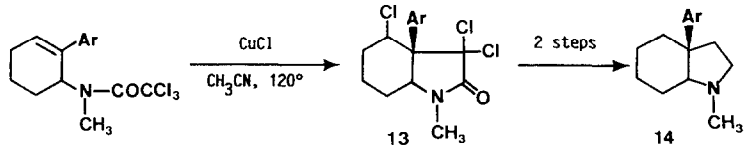


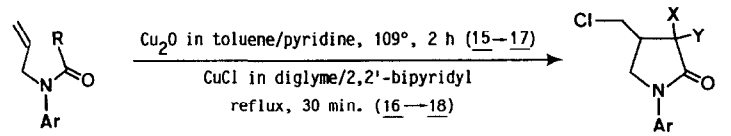
To illustrate this point, Minisci prepared as early as 1963 1,2,2-trichloropropene (2), a synthetic equivalent of malonic dialdehyde, from the 1:1-adduct 1 of chloroform and vinylchloride, albeit in low yield (20 %).[10] It is noteworthy, however, that the conventional free-radical chain process does not afford 1 because the low transfer constant of $CHCl_3$ cannot prevent the polymerisation of vinyl chloride,[5b] and in any case it would have led to the isomeric 1,1,1,3-tetrachloropropane. Sato et al.[11] used the copper-catalysed addition of CCl_4 to isobutylene in the presence of n-butylamine as ligand for the preparation of the natural product 3-methyl-2-butenoic acid (4, 'senecioic acid') in 70-80 % overall yield. The yield of the 1:1-adduct 3 is comparably high using e.g. CuI (86 %), CuBr (75 %), CuO_2 (85 %), $CuCl_2$ (83 %) and $Cu(NO_3)_2 \cdot 3\ H_2O$ (83 %) as catalyst.



Cu-catalysed reactions show definite advantages, especially on an industrial scale, due to the simplicity of the reaction systems. Thus, the acid moiety 7 of the pyrethroids[12] which are highly potent insecticides, can be prepared steroselectively (cis:trans >4:1) by a short conceptually unprecedented route involving the 1:1-adducts 5 (R = Cl, 76 % yield; R = CF_3, 40 % yield), which serve as precursors of the very reactive ketenes 6.[6c,13] Recently, the cyclopropane carboxylic acids 7 (R = CF_3; cis:trans 1:1), 10 and 12 were synthesised via the corresponding 1:1-adducts 8 (83 % yield),[14] 9 (85 % yield),[15] and 11 (54 % yield),[16] respectively. The latter reaction, as well as Itohs's[17] elegant stereoselective route to dl-mesembrane 14 (Ar = 3,4-$(CH_3O)_2C_6H_3$) via 13 (47 % yield of cyclisation) represent interesting extensions of the efficient Cu-catalysed cyclisation of N-allyl di- and -trihaloacetamides 15 and 16, respectively. Their intramolecular ring closures were used for the preparation of large numbers of 4-chloromethyl-2-pyrrolidinone derivatives, e.g. 17 (73 %)[18] and 18 (87 % yield),[19] which are selective herbicides for weed control.

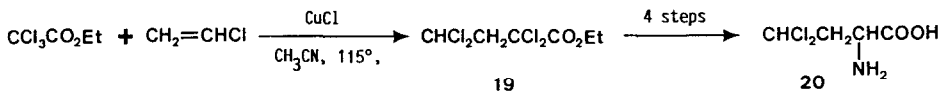
The very easy synthesis of the known natural antibiotic α-aminoacid armentomycin (20) in 50 % overall yield[20] in its d,l-form via the 2,2-dichlorosubstituted ester 19 (79 %)[6c] concludes this short survey of known synthetic applications of the Cu-catalysed addition reaction.





15 R = CCl_3
16 R = CHFCl

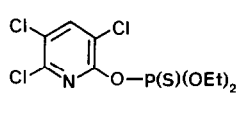
17 X = Y = Cl
18 X = H, Y = F



In this paper we report new approaches to three classes of heterocycles, involving a Cu-catalysed addition of small organic polyhalides to activated olefins as a key carbon-carbon bond forming step. In addition, some synthetically useful transformations of products and intermediates thus formed are described.

HALOGENATED PYRIDINES

Chlorinated and fluorinated pyridines are valuable intermediates for the preparation of various biologically active substances, particularly insecticides, herbicides and fungicides, e.g. DURSBAN (21)[21] and ALFACRON (22),[22] two insecticides in the class of phosphoric esters, both with a chlorinated pyridine moiety; TOPIC (23),[23] a herbicide with a phenoxy substituted 3,5-dichloropyridine as the biocidal structural element; chlorfluazuron (25),[24] a new insecticide and CGA 143268 (23),[25] a new fungicide, two highly active compounds containing the 3-chloro-5-trifluoromethylpyridine moiety. It is not surprising that in industrial laboratories there are intensive activities to find good ways of synthesising halogenated pyridines.



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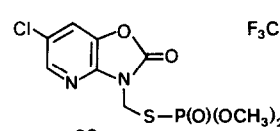

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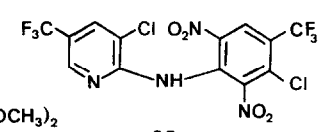

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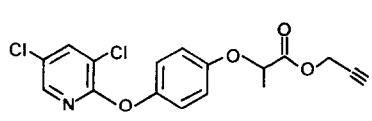

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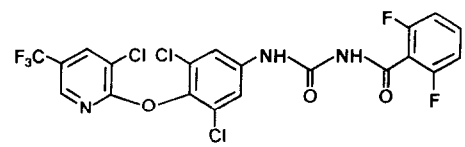

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When we first considered halogenated pyridines as a synthetic target, we set as our goal the development of a strategy that would not only allow the introduction of chlorine but also of any alkyl group in the 5-position of the 2,3-dichloropyridine. This requirement can be realised by taking advantage of the easily achieved Cu-catalysed addition of chloral and of 2,2-dichloroaldehydes to acrylonitrile and to methacrylonitrile. Between 105° and 130°, the 1:1-adducts 27 are formed with acrylonitrile as the olefinic component.

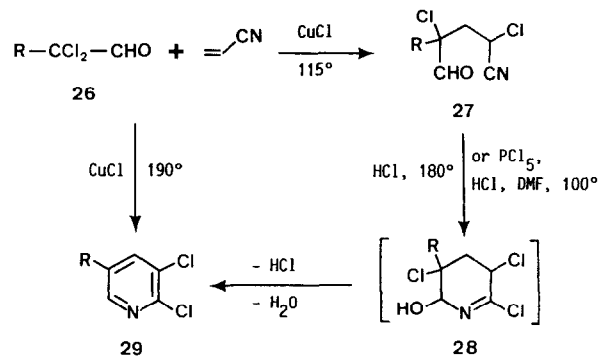


Table 1. Conversion of 2,2-dichloroaldehydes 26 to pyridines 29 in the presence of CuCl (6 mol %) in MeCN at 190°C in 30 min.

Aldehyde[a]	R	Yield (%)[b]	Mp./Bp.	^{1}H-NMR ($CDCl_3$) H-C(4), d, 2 Hz	H-C(6), d, 2 Hz
26a	Cl	65[c]	49-51°	7.80	8.28
26b	CH_3	53	46-47°	7.59	8.13
26c	CF_3	60	80°/20 mm	8.03	8.63
26d	CH_2-CH_3	49	72°/0.1 mm	7.55	8.08
26e	CH_2-CH_2Cl	57	97°/0.1 mm	7.60	8.10
26f	CH_2-$CHCl_2$	50	89-90°	7.70	8.18
26g	CH_2-CCl_3	46	90°	7.85	8.35
26h	n-C_3H_7	35	78°/0.01 mm	7.55	8.08
26i	i-C_3H_7	33	54°/0.06 mm	7.70	8.25
26k	n-C_4H_9	52	84°/0.2 mm	7.60	8.15
26l	n-C_5H_{11}	51	105°/0.06 mm	7.80	8.30

a) For the preparation of the aldehydes 26b - 26l see experimental part. b) Isolated yields. c) See ref. 26.

As envisaged, the 1:1-adducts 27 may be transformed to the pyridines 29 if they are heated at 180°, most advantageously in the presence of a flow of hydrogen chloride, or, if they are treated at 75-100° with phosphorus pentachloride in DMF, which is saturated with hydrogen chloride. In an enamel autoclave at 190°, the pyridines 29 are directly formed in a one-pot process involving 27 and 28 as intermediates in 33 to 65 % yield (table 1). The influence of the catalyst in the one step preparation of the pyridines 29 is shown in table 2 as an example of the addition of chloral to acrylonitrile: highest yields are obtained by CuCl and copper powder. Of the other catalysts, only rutheniumtris-triphenylphosphine dichloride produces 2,3,5-trichloropyridine 29a in a moderate yield.

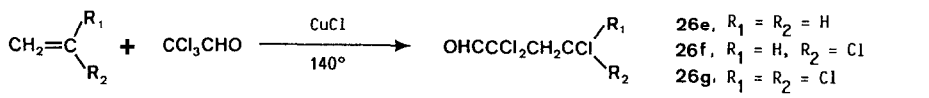
Table 2. Influence of the catalyst in the one step synthesis of 29a.

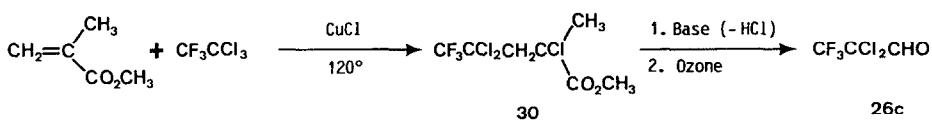
Catalyst	Cu[a)]	CuCl	$RuCl_2(P\emptyset_3)_3$	NiCl	$FeCl_2$	$ZnCl_2$	$MnCl_2$
Yield (%)[b)] on 29a	57	65	44	2	2	10	6

a) Copper powder, activated using the process described for copper bronze.[27]

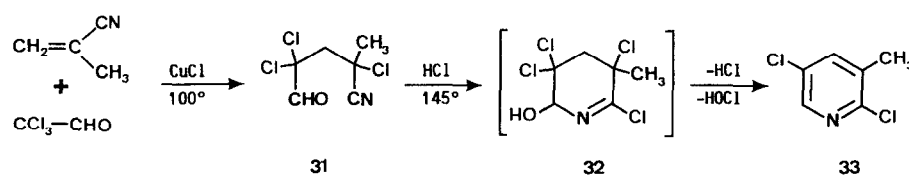
b) Standard experimental conditions were used, see table 1.

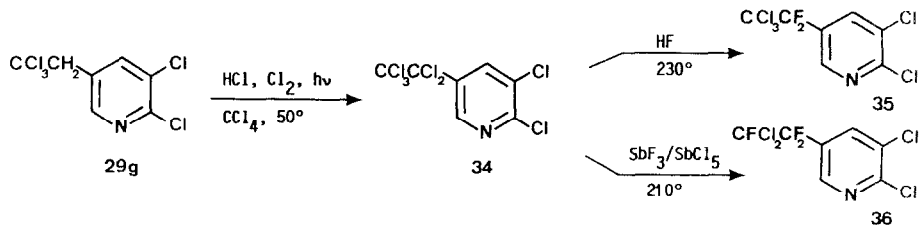
The 2,2-dichloroaldehydes used in the Cu-catalysed additions to acrylonitrile were prepared according to knwon procedures (chlorination in DMF, see exp. part).[28] For the preparation of the 2,2-dichloroaldehydes with additional halogen atoms in position 4, again the CuCl-catalysed addition is a good access: trichloroacetaldehyde is added at 140° to ethylene, to chloroethylene and to 1,1-dichloroethylene. After distillation, the aldehydes 26e, 26f and 26g are isolated in 68, 71 and 41 % yield, respectively. The novel 2,2-dichloro-3,3,3-trifluoropropionaldehyde (26c),[29] which is the starting material for the introduction of the CF_3-group into the 5-position of pyridine, can be prepared from methyl 4,4-dichloro-5,5,5-trifluoro-2-methyl-2-pentenoate[30] by ozonolysis, followed by reductive work-up.





In view of the mechanism of the cyclisation/elimination step of the open chain 1:1-adduct 27 to pyridines 29, the following experiment is noteworthy: the CuCl-catalysed addition of chloral to methacrylonitrile affords the expected 4-formylonitrile 31 in 64 % yield. In the 2-position of this nitrile, there is no hydrogen for a 1,4-water-elimination after cyclisation to 32. In spite of this, aromatisation to pyridine 33 occurs easily, probably via elimination of HOCl. The one-pot addition-cyclisation-aromatisation process is possible in this case also, affording the pyridine 33 in 65 % yield.





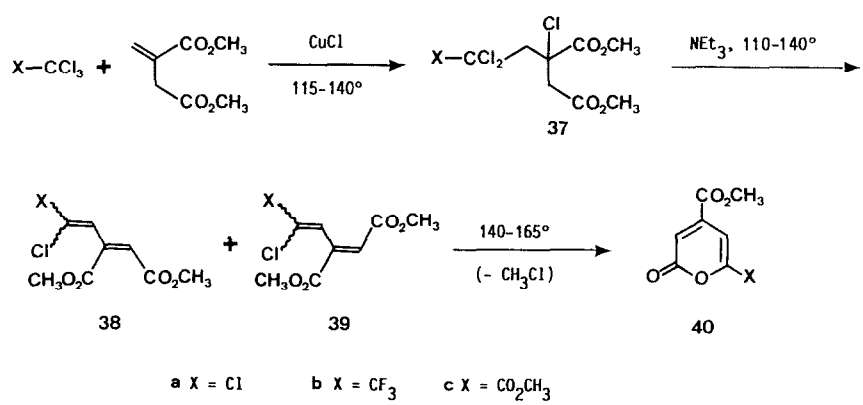
The importance of chlorinated pyridines with poly-halogenated alkyl side chains was emphasized in the introduction. A further halogenation of the side chains of pyridines 29 (R = alkyl, haloalkyl) is easily possible, as shown in the case of 29g. The chlorination affords pyridine 34 (76 % yield) with the fully chlorinated ethyl-group. The selective exchange of the chlorine atoms in the side chain of 34 can be achieved, e.g. by treatment of 34 with hydrogen fluoride at 230°, which gives rise to the pyridine 35 (65 %) with the 2',2'-difluoro-3',3',3'-trichloroethyl group in 5-position. Using a $SbF_3/SbCl_5$-mixture as a fluorinating agent (see exp. part), a third chlorine of the side chain is exchanged, affording 36 as the main product.

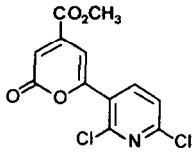
α-PYRONES

The α-pyrone moiety appears in several natural products, e.g. cardiac glycosides of the scilla group and also among the toad-toxins,[31] paracotoine, 5,6-dehydrokawaine, yangonine, anibine and bispidine,[32] to mention but a few. Furthermore, α-pyrones are versatile intermediates for the synthesis of pyridines.[33] Their propensity to undergo the Diels-Alder reaction makes them useful for syntheses of highly substituted aromatics,[34] biphenyles,[35] natural products[36] and barrelen.[37] 6-Chloro-α-pyrones show the property of inactivating enzymes.[38]

The Cu-catalysed addition of CCl_4 to methyl itaconate is an especially clean reaction which leads to the 1:1-adduct 37a in 93 % yield (in the presence of 3-6 mol % CuCl at 115°). Double HCl-elimination with triethylamine in boiling toluene affords the dienes 38a/39a (92 %; the ratio maleate 38a:fumarate 39a is 6:94 according to ^{1}H-NMR). Refluxing a solution of 38a/39a in xylene leads to elimination of CH_3Cl[39] and formation of 6-chloro-4-methoxycarbonyl-α-pyrone (40a) in 81 % yield.

1,1,1-Trichloro-2,2,2-trifluoroethane and methyl trichloroacetate can be added to methyl itaconate in a similar way to give 37b and 37c (57 and 90 % yield, respectively).

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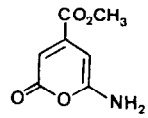
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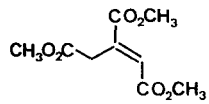
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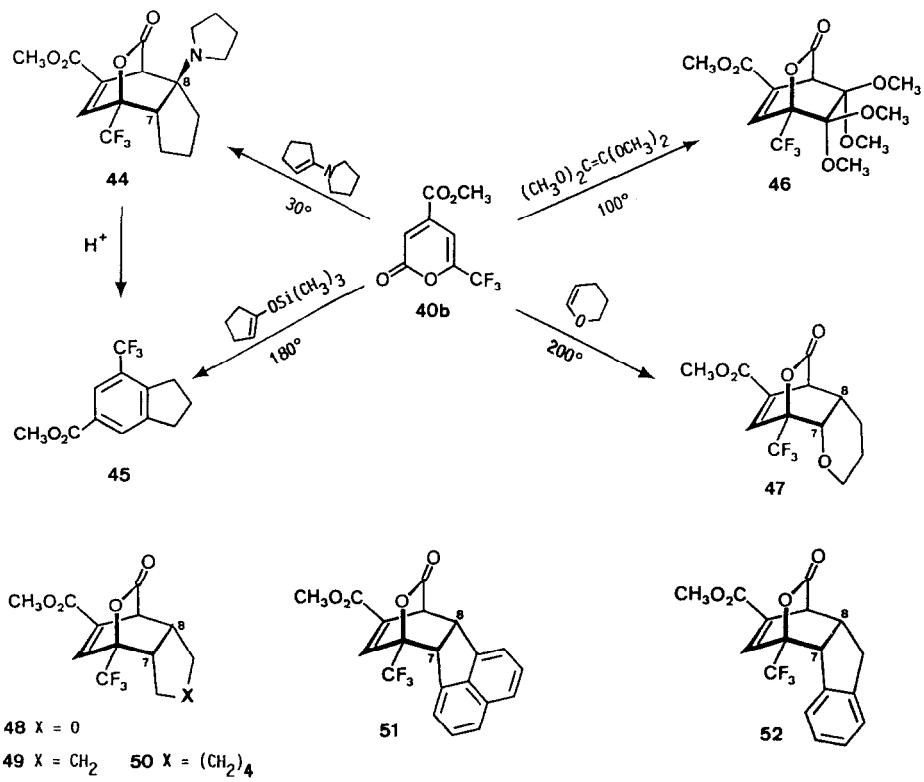
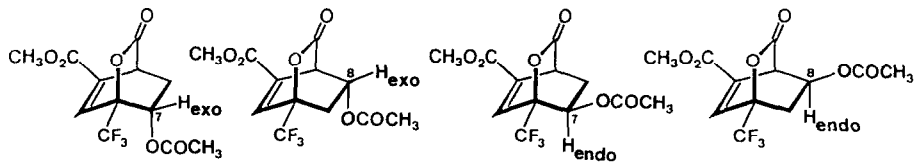
Elimination of HCl from the adducts 37b and 37c affords the dienes 38b/39b and 38c/39c (ratio maleate:fumarate 17:83 and 20:80, respectively). The E/Z-configuration of the double bonds substituted by chlorine, CF_3- or CH_3O_2C-group, respectively, in 38b, 38c, 39b and 39c has not been established, but both maleates as well as fumarates are configuratively homogeneous. On heating the mixture of isomers 38b/39b in mesitylene, 4-methoxy-6-trifluoromethyl-2H-pyran-2-one (40b) is formed (62 %). Using similar conditions, α-pyrone 40c can be prepared, albeit in low yield (12 %).

From the complex reaction mixture arising from the CuCl-catalysed addition of 2,6-dichloro-3-trichloromethylpyridine to methyl itaconate, no open chain adduct can be isolated. Instead, the pyridino-α-pyrone 41 crystallizes out in 18 % yield.

Due to the chlorine atom in 6-position, the α-pyrone 40a becomes a vinylogous acid chloride and loses thereby the typical reactivity of α-pyrones. C(6) and not C(2) is now the most electrophilic carbon atom. As a consequence, the 6-chloro substituent in 40a can be replaced by a great variety of nucleophiles; e.g. with ammonia, the yellow 6-amino-α-pyrone 42 is formed (71 %). With various anilines 40a does not react to the corresponding pyridine derivatives[40] but to give the 6-anilino-α-pyrones. Treatment of 40a with methanol causes ring opening to the triester 43 in 88 % yield.



The presence of the carbomethoxy- and CF_3-groups in the diene system of the pyrone 40b increases its electrophilicity and its ability to undergo Diels-Alder reactions with inverse electron demand. The reaction of 40b with 1-(N-pyrrolidino)-1-cyclopentene at 30° gives rise to the tricyclic lactone 44 (92 %). When 44 is treated with HCl/dioxane, the indane derivative 45 is obtained in 51 % yield. Thus, 1-(N-pyrrolidino)-cyclopentene may be regarded as a synthetic equivalent of the elusive cyclopentyne. Compound 45 is obtained directly in the reaction of 40b with 1-trimethylsilyloxycyclopentene at 180° (90 %). Whereas the very nucleophilic tetramethoxyethylene adds (at 100°) to 40b to afford 46 (71 %), attempts to add 'classic' dienophiles such as TCNE and maleic anhydride to 40b failed. 46 represents the first Diels-Alder adduct of tetramethoxyethylene with a cyclic diene known to date. With 3,4-dihydro-2H-pyrane at 200°, 47 is formed as the sole regioisomer (81 %). Endo-adducts of this type result also with 2,5-dihydrofuran (48; 130°; 71 %), cyclopentene (49; 120°; 92 %), cyclooctene (50; 150°; 87 %) and acenaphthylene (51; 100°; 89 %). Compound 52, formed from 40b and indene at 80° (87 %), contains the methylene group attached exclusively endo to C(8). All four possible regio- and stereoisomers can be identified in the NMR-spectrum of 53, the product of reaction of 40b with vinylacetate at 150° (79 % yield).

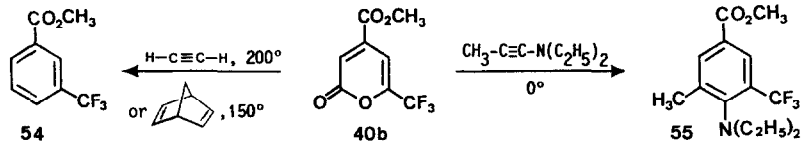


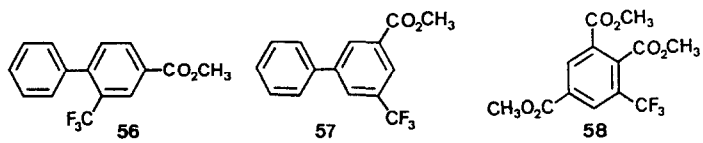
53a 53b 53c 53d

The presence of the 3-oxo-2-oxabicyclo[2.2.2]oct-5-ene moiety in the Diels-Alder adducts of 40b with olefins is easily detected by the strong carbonyl absorption (1790-1800 cm^{-1}) in the IR-spectra. Furthermore the configuration of the bicyclic and tricyclic adducts is based on their ^1H- and proton coupled ^{13}C-NMR spectra. In detail, the assignment of the four isomers 53a-d was carried out in the following manner. The coupling constants between H-C(4) and H-C(8) show whether the OAc group occupies position 7 or 8, since the vicinal coupling constants between H-C(4) and both H_{endo}-C(8) and H_{exo}-C(8) are nonzero and of about the same magnitude in this bicyclic system.[41,42] The exo/endo position of the OAc group can be assigned with the aid of the chemical shift of its geminal proton (H-C(7) or H-C(8)), since this proton absorbs at lower field in the exo position.[42] This can be corroborated by comparing the vicinal coupling between C(3) and H-C(8) in 53b (1.2 Hz) with that in 53d (8.2 Hz), corresponding to a dihedral angle of ca. 80° in 53b and of almost 180° in 53d (for the analogous argumentation in the case of [2.2.1]bicycloheptanes, see ref. 43).

Similarly, the coupling between C(3) and H-C(8) was used for the assignment of the configurations of 47 (J=2.7 Hz), 48 (J=2.0 Hz), where the assignment of the proton couplings of C(3) was verified with low power selective decoupling of H-C(4), H-C(6) and H-C(8), respectively, and 49 (J<2 Hz). Moreover, $^3J_{C(5),H-C(8)}$ amounts to 7.0 Hz in 47 and to 7.5 Hz in 48 as expected from the antiperiplanar arrangement of the coupled nuclei. The endo position of the carbocyclic ring anellated at C(7) and C(8) in 49-52 was easily shown by Lanthanide induced shift (LIS) experiments, comparing the induced shifts of H-C(4) and H-C(6) with those of H-C(7) and H-C(8). In 44, however, the additional pyrrolidine ring precluded the use of LIS experiments. The assignment of the configuration, therefore, was carried out by comparing the ^{13}C chemical shifts of 44 with those of 49. The shifts of C(5) and C(6) are virtually indentical in both compounds. Consequently, the pyrrolidine ring occupies an exo position since the N atom would polarize the double bond inducing chemical shift changes in the double bond C atoms (compare e.g. C(2) and C(3) in 5-endo-methyl-bicyclo[2.2.2]oct-2-ene (134.1 and 132.0 ppm) with those of the corresponding 5-endo hydroxy compound (135.9 and 129.9 ppm)[44]). The small γ-effect observed for C(3) (168.4 ppm in 44 vs. 169.5 ppm in 49) is in agreement with an 8-exo position of the pyrrolidine ring, position 8 being obvious from the absence of a coupling between H-C(4) and the methine proton of the cyclopentane ring.

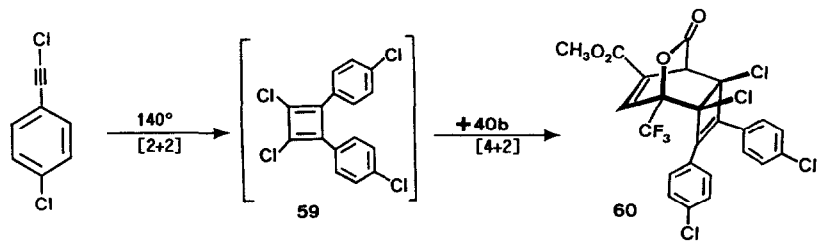
Another feature of 40b is its ability to undergo Diels-Alder reactions with acetylenes. The cycloadducts decarboxylate spontaneously to form benzene rings bearing the CF_3-group. The substitution pattern is determined by the regioselectivity of the [4+2]-cycloaddition step. Thus, the reaction of 40b with 1-(N,N-diethyl-amino)-1-propyne takes place at 0° to produce 55 as a single isomer in 68 % yield. The reversal of the regioselectivity of 44 vs. 55 is remarkable and cannot be explained by the interaction of the LUMO of the diene 40b and the HOMO of the enamine in the case of the addition to 44.[45]





Less electron rich acetylenes require reaction temperatures of 140° to 200°. Treatment of 40b with acetylene at 200° leads to 54 (91 %). Heating of 40b with norbornadiene (instead of acetylene) at 150° initiates a cascade of pericyclic reactions of one [4+2]-cycloaddition and two subsequent retro [4+2]-cycloadditions (elimination of CO_2 and cyclopentadiene), which gives rise to 54 in 90 % yield. Phenylacetylene affords a 3:2 mixture of biphenyls 56 and 57 (39 %). With dimethyl acetylenedicarboxylate 58 is formed (67 %).

However, with 1-chloro-2-(4'-chlorophenyl)acetylene in boiling xylene the expected derivative of biphenyl is not formed. Instead, the tricyclic cyclobutene 60 can be isolated as the sole product in 70 % yield. The structure of 60 was established by X-ray structure analysis (see figure 1).[46] This surprising result indicates that 1-chloro-2-(4'-chlorophenyl)acetylene presumably first undergoes a head-to-head [2+2]-cycloaddition reaction[47] leading to the highly reactive 1,2-dichloro-3,4-di(4'-chlorophenyl)cyclobuta-1,3-diene, which is immediately captured by the diene 40b across its least sterically hindered bond.[48]



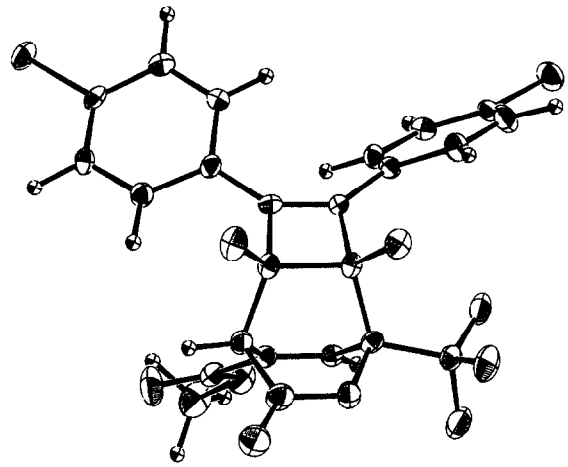
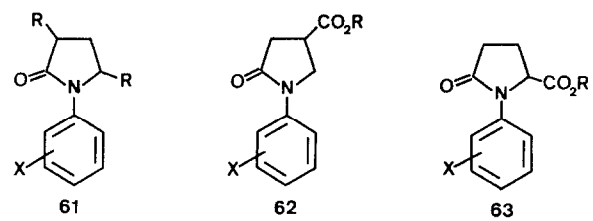


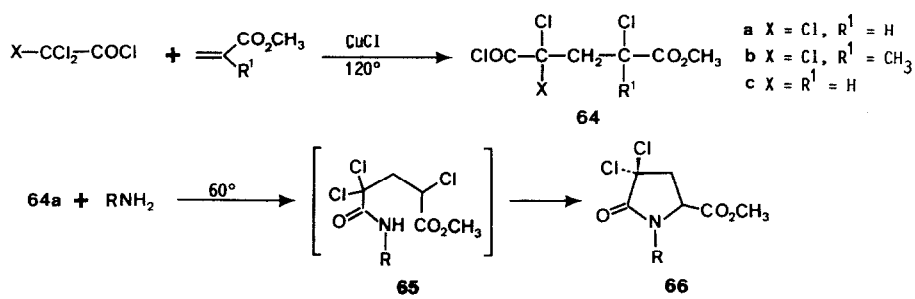
Fig. 1
ORTEP drawing of 60.

N-ARYL DERIVATIVES OF THE CYCLIC AMIDE OF GLUTAMIC ACID

Some N-aryl substituted pyrrolidine-2-ones, e.g. 17, 18 as well as 61 (R = H, alkyl)[49] are known as herbicides, also N-aryl substituted pyrrolidine-2-one-4-carboxylic acid derivatives 62 are substances for influencing plant growth.[50] The isomeric 5-carboxylic acid derivatives 63 (N-aryl substituted pyroglutamic acids) as well as N-aryl substituted proline derivatives are novel compounds.[51] For that reason, we were interested in a generally practicable synthesis of N-substituted pyroglutamic acids.



61 62 63



64

64a + RNH_2 → 65 → 66

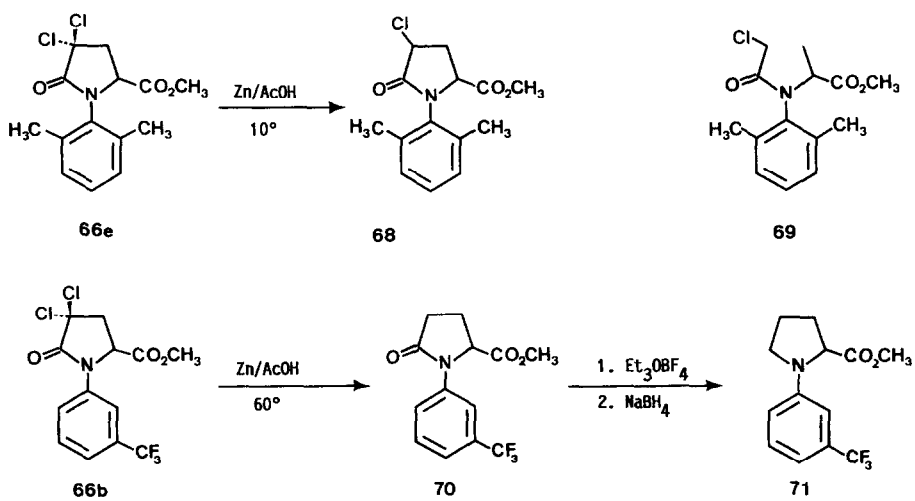
Once again, the key carbon-carbon bond formation step is the CuCl-catalysed addition of a halogenated C_2-unit to activated olefins: this time the addition of dichloro- and trichloroacetyl chloride to methyl acrylate or to methyl methacrylate affords the highly functionalised 1:1-adducts 64. Compound 64a is cyclized with primary amines at 60° in the presence of triethylamine to the N-substituted 3,3-dichloro-pyroglutamic ester 66 (see table 3). Only in the reaction of 64a with ammonia at 6° was the open chain amide 65 (R = H) isolated prior to the cyclisation (at 80°) to the novel methyl-3,3-dichloropyroglutamate 66o, a precursor for the preparation of the d,l-pyroglutamic acid.

Table 3. Reactions of 64a with primary amines R-NH_2 to 66.

66	R	Yield (%)	mp. (°C)
a	phenyl	92	123-124
b	3-CF_3-phenyl	87	58-59
c	4-Cl-phenyl	90	107
d	3,5-$(CF_3)_2$-phenyl	75	93
e	2,6-$(CH_3)_2$-phenyl	84	99
f	2-CH_3,4-Cl-phenyl	97	113
g	3-Cl,4-CH_3-phenyl	80	74-75
h	3,5-$(CH_3)_2$-phenyl	77	97-98
i	3,5-Cl_2-phenyl	95	138
k	4-i-C_3H_7-phenyl	93	88-89
l	2-NO_2-phenyl	86	112-113
m	$CH(CH_3)_2$	53	127-128[b]
n	NH-$CO_2C_2H_5$	65	100-102
o	H	54[a]	96-97

a) Via amide 65, R = H (100 %, mp. 77-78°). b) Bp. at 0.4 mm.

With water, 64a reacts cleanly to the lactone of 2,2-dichloro-4-hydroxy-4-methoxycarbonyl-butyric acid (67) in 88 % yield,[52] see experimental part. Partial dechlorination of 66e with zinc in acetic acid at 10° leads to the cis/trans-isomeric mixture of the monochloroglutamates 68, which are seco-analogues of the known acylalanine fungicide 69[53] which is very efficient for the control of tobacco blue mold. The fully dechlorinated compounds can be obtained by reduction with zinc at 60°, e.g. 66b to 70 in 84 % yield. The dechlorinated methyl N-arylpyroglutamates can be transformed to the corresponding novel N-arylproline derivatives by the one-pot method of Menteiro,[54] as exemplified by the conversion of 70 to 71 in 49 % yield.



CONCLUSIONS

The characteristic, and preparatively very useful, features of Cu(I)-catalysed addition of organic polyhalides to olefins, namely: (a) the simplicity of the reaction system; (b) the high 1:1 selectivity of the addition; and (c) the sufficient functionality, allow considerable synthetic manipulation of the 1:1-adducts. The reaction can be widely applied to the construction of many cyclic systems, e.g. α-pyrones, halogenated pyridines and cyclic amides of glutamic ('pyroglutamic') acid. It is evident that the underlying reaction has a broad scope and represents a versatile synthetic tool for both laboratory and industrial use.

EXPERIMENTAL

General remarks. Mps and bps (°C) are not corrected; IR (ν [cm^{-1}]), Perkin Elmer 298; ^{1}H- and ^{13}C-NMR, Bruker WM 250, Bruker WM 400, Varian T 60, Varian HA 100, Varian XL 100 and Varian XL 300, abbreviations according to the IUPAC Commission[55]; satisfactory microanalyses were obtained for all products; procedures reported have not always been optimised.

Preparation of the 2,2-dichloroaldehydes 26b, 26d, 26h-26l; general procedure.[28] Chlorine is bubbled into a solution of DMF (200 ml) and HCl (10 g). A solution of the aldehyde (1 mol) in DMF (300 ml) is added dropwise at 65°. During this time chlorine (70 g) is introduced in a stream. The mixture is heated at 65° for an additional hour and then steam distilled. The organic layer of the distillate is separated and rectified: 26b, 83 %, bp. 68-72°/760 mm (lit.[28]: 86°/760 mm); 26d, 76 %, 30-32°/30 mm (Lit.[28]: 116-118°/760 mm); 26h, 84 %, 60-63°/60 mm; 26i, 83 %, 39-41°/35 mm; 26k, 81 %, 59-61°/ 21 mm; 26l, 46 %, 70-72°/15 mm.

2,2-Dichloro-3,3,3-trifluoro-propionaldehyde (26c). Ozone (19.2 g, 0.4 mol) is bubbled into a solution of the methylester of 4,4-dichloro-5,5,5-trichloro-2-methylpent-2-ene-carboxylic acid[30] (100.4 g, 0.4 mol) in acetic acid (800 ml) at 20°. Afterwards, zinc powder (15 g) and water (15 ml) are added and the aldehyde 26c thus obtained is distilled off: 52.8 g (72 %), bp. 66-67°/760 mm; IR (CCl_4): 1770 (CO). ^{1}H-NMR ($CDCl_3$): 9.3 (q, J_{HF}=2.5). ^{13}C-NMR ($CDCl_3$); 178.6 (CH=O, J_{CH}=206); 120.8 (CF_3, J_{CF}=284); 80.1 (CCl_2, J_{CF}=34).

Preparation of 2,2-dichloroaldehydes 26e-26g: Addition of trichloroacetaldehyde to ethylene, chloroethylene and 1,1-dichloroethylene. Trichloroacetaldehyde (147.5 g, 1 mol), the olefin (2 mol), CuCl (3 g, 0.03 mol) and acetonitrile (300 ml) are heated for 4 hours at 140° in an enamel autoclave. After cooling the reaction mixture, the solvent is evaporated and the residue is distilled: 26e, 68 %, bp. 64-66°/15 mm; 26f, 71 %, bp. 78-80°/12 mm; 26g, 41 %, 95-98°/15 mm.

One step preparation of pyridines 29; general procedure. The 2,2-dichloroaldehyde 26 (1.2 mol), acrylonitrile (1 mol) and CuCl (0.5 g, 0.05 mol) are heated in acetonitrile (400 ml) for 0.5 hour at 190° in an enamel autoclave. After cooling the solvent is distilled off. The residue is subjected to steam distillation. Yields, mp. or bp. and ^{1}H-NMR-dates are given in table 1.

Preparation of 2,3,5-trichloropyridine (29a) from 2,4,4-trichloro-4-formylbutyronitrile (27, R=Cl). Phosphorus pentachloride (10.3 g, 0.05 mol) is added portionwise at a maximum of 60° to DMF (40 g). The solution obtained is subsequently saturated with hydrogen chloride, whereupon the temperature rises to 95°. After cooling to 50° compound 27 (R=Cl)[26] (20 g, 0.1 mol) is addes dropwise in such a manner, that a temperature of 75° is not exceeded. After completion of the addition of the aldehyde, the mixture is heated at 100° for 1 hour. The reaction mixture at 60° is subsequently poured onto ice, whereupon 29a precipitates: 16.2 g (89 %), mp. 49-51°. ^{1}H-NMR see table 1.

4-Formyl-2-methyl-2,4,4-trichlorobutyronitrile (31). Trichloroacetaldehyde (14.7 g, 0.1 mol), methacrylonitrile (13.5 g, 0.2 mol), CuCl (0.3 g, 3 mmol) and acetonitrile (30 ml) are heated in an enamel autoclave for 15 hours at 100°. After cooling, the solvent is distilled off; diethylether (500 ml) is added to the residue and the precipitated CuCl is filtered off. The evaporated residue is rectified. The fraction boiling at 76-78°/0.05 mm is collected: 13.8 g (64 %) 31. IR (neat): 2250 (CN), 1750 (CO). ^{1}H-NMR ($CDCl_3$): 2.06 (s, CH_3), 3.18 and 3.30 (AB, J=15, H_2-C(3)); 9.20 (s, -CH=O).

Preparation of 2,5-dichloro-3-methylpyridine (33). a) from 31: Compound 31 (21.4 g, 0.1 mol) is introduced dropwise during 15 minutes into a vertical jacket tube which is 40 cm long and 2.5 cm wide and which is half filled with Raschig rings, the jacket of the tube being heated with hot oil at 175-185°. Simultaneously a weak flow of hydrogen chloride is introduced into the reactor. The dark resin dripping from the reaction vessel is distilled with steam: 9.9 g (61 %) 33, mp. 42°. ^{1}H-NMR ($CDCl_3$): 2.40 (s, CH_3); 7.50 (d, J=2, H-C(4)); 8.15 (d, J=2, H-C(6)). ^{13}C-NMR (DMSO-d_6): 148.8 (C(2)); 145.3 (dd, C(6)); 139.4 (ddq, C(4)); 134.1 (C(3)); 130.0 (C(5)); 18.8 (qd, CH_3); multiplicities given for the proton coupled spectrum. b) one step preparation: Trichloroacetaldehyde (14.7 g, 0.1 mol), methacrylonitrile (13.5 g, 0.2 mol), CuCl (0.5 g, 5 mmol) and acetonitrile (40 ml) are heated in an enamel autoclave for 2 hours at 150°. The solvent is distilled off and the residue is steam distilled: 10.5 g (65 %) 33, mp. 41-42°.

2,3-Dichloro-5-(pentachloroethyl)-pyridine (34). To a cold solution of 29g (279.4 g, 1 mol) in CCl_4 (3 l) hydrogen chloride (120 g) is added. The heterogenous reaction mixture is kept at 50° and under UV irradiation (125 W high pressure Hg lamp) while a stream of chlorine is introduced. After 2 hours, the solvent is distilled off and the residue is crystallised from methanol: 264.8 g (76 %) 34, mp. 98°. ^{1}H-NMR ($CDCl_3$): 8.40 (d, J=2, H-C(4)); 8.93 (d, J=2, H-C(6)). ^{13}C-NMR ($CDCl_3$): 151.3 (C(2)); 148.6 (C(6)); 140.6 (C(4)); 131.9 (C(5)); 129.4 (C(3)); 104.2 (CCl_3); 94.8 (CCl_2).

2,3-Dichloro-5-(1,1-difluoro-2,2,2-trichloroethyl)-pyridine (35). In an enamel autoclave compound 34 (104.4 g, 0.3 mol) and hydrogen fluoride (300 g) are heated for 10 hours at 230°. After cooling and evaporation of hydrogen fluoride, the content of the autoclave is poured into ice water (2.5 l). The crystals are collected and washed with water and ethanol. The crude product (102.8 g) is chromatographed on silica gel (petrolether:HCl_3 - 60:40). The first fractions afford 66.3 g (65 %) 35, mp. 54-55°. ^{1}H-NMR ($CDCl_3$): 8.05 (d, J=2, H-C(4)); 8.58 (d, J=2, H-C(6)). ^{13}C-NMR ($CDCl_3$): 152.6 (C(2)); 146.9 (C(6)); 138.6 (C(4)); 130.4 (C(3)); 126.2 (C(5), J_{CF}=27); 116.4 (CF_2, J_{CF}=261); 96.3 (CCl_3, J_{CF}=40). The second fraction contains 32.8 g (32 %) 3-chloro-5-(1,1-difluoro-2,2,2-trichloroethyl)-pyridin-2-one, mp. 232-234°. IR (KBr): 1665 (CO). ^{1}H-NMR (DMSO-d_6): 7.92 (d, J=2, CH); 7.98 (d, J=2, CH); 12.94 (s, NH). ^{13}C-NMR ($CDCl_3$): 157.8 (C(2)); 137.1 (C(6)); 136.4 (C(4)); 124.4 (C(3)); 116.9 (CF_2, J_{CF}=259); 106.1 (C(5), J_{CF}=29); 96.5 (CCl_3, J_{CF}=42).

2,3-Dichloro-5-(1,1,2-trifluoro-2,2-dichloroethyl)pyridine (36). A mixture of 34 (348 g, 1 mol), SbF_3 (1000 g) and $SbCl_5$ (30 g) is fused at 210°. After 2 hours, the reaction mass is cooled to 90°

and H_2O (2 l) is added. After steam distillation, the oil obtained is dried with Na_2SO_4 and rectified: 203.2 g (68 %) 36, bp. 119-121°/10 mm. ^{1}H-NMR ($CDCl_3$): 8.03 (d, J=2, H-C(4)); 8.55 (d, J=2, H-C(6)). ^{13}C-NMR ($CDCl_3$): 153.1 (C(2)); 146.2 (C(6)); 137.8 (C(4)); 131.0 (C(3)); 126.1 (C(5)); 116.6 ($CFCl_2$, $^1J_{CF}$=303, $^2J_{CF}$=40); 115.2 (CF_2, $^1J_{CF}$=260, $^2J_{CF}$=31).

Methyl-3-methoxycarbonyl-3,5,5,5-tetrachloropentaneoate (37a). Dimethyl itaconate (790 g, 5 mol), CCl_4 (4.5 l), acetonitrile (2 l) and CuCl (33 g, 0.33 mol) are heated together in an enamel autoclave for 24 hours at 115°. The reaction mixture is filtered and evaporated. The residue is distilled (short path): 1457 g (93 %) 37a, bp. 100°/0.01 mm. IR (neat): 1745 (CO). ^{1}H-NMR ($CDCl_3$): 3.40 (s, CH_2); 3.70 (s, OCH_3); 3.80 (s, OCH_3); 3.84 (s, CH_2).

Methyl-3-methoxycarbonyl-3,5,5-trichloro-6,6,6-trifluorohexanoate (37b). Dimethyl itaconate (222 g, 1.4 mol), 1,1,1-trichloro-2,2,2-trifluoroethene (400 g, 2.13 mol), acetonitrile (250 ml) and CuCl (7.9 g, 0.08 mol) are heated in a 2.5 l tantalum autoclave. After evaporation and filtration, distillation yields 280.3 g (57 %) 37b, bp. 80-85°/0.3 mm. IR (neat): 1755 (CO). ^{1}H-NMR ($CDCl_3$): 3.40 and 3.47 (AB, J=16, H_2-C(4)); 3.42 and 3.52 (AB, J=17.5, H_2-C(2)); 3.73 and 3.86 (each s, each OCH_3).

Dimethyl-3-methoxycarbonyl-3,5,5-trichloroadipinate (37c). Dimethyl itaconate (158 g, 1 mol), methyltrichloroacetate (400 ml), 3-methoxypropionitrile (150 ml) and CuCl (6 g, 0.06 mol) are heated together for 24 hours at 125°. The filtered and evaporated reaction mixture is distilled: 301 g (90 %) 37c, bp. 143-145°/0.2 mm, mp. 75° (hexane/ether). IR ($CHCl_3$): 1740 (CO). ^{1}H-NMR ($CDCl_3$): 3.19 and 3.40 (AB, J=17, H_2-C(2)); 3.55 and 3.64 (AB, J=15, H_2-C(4)); 3.74, 3.86 and 3.92 (each s, each OCH_3).

Preparation of 38 / 39; general procedure: Compound 37c (2 mol) in toluene or xylene (900 ml) is added dropwise to a solution of triethylamine (455 g, 4.5 mol) in toluene or xylene (1.5 l). The reaction mixture is refluxed for 4 hours, then filtered and the filtrate is washed with H_2O, dried ($MgSO_4$) and evaporated. Distillation of the residue yields 92 % 38a / 39a, 78 % 38b / 39b and 89 % 38c / 39c.

38a / 39a = 6:94, bp. 100°/0.03 mm (short path distillation). IR (neat): 1735 (CO). ^{1}H-NMR ($CDCl_3$) of 39a: 3.78 and 3.86 (each s, each OCH_3); 6.66 (d, J=2, H-C(4)); 7.11 (d, J=2, H-C(2)). The olefinic protons of the isomer 38a are visible at 6.16 and 6.52 (each d, J=1.3).

38b / 39b = 17:83, bp. 59-61°/0.2 mm. IR (neat): 1740 (CO). ^{1}H-NMR ($CDCl_3$) of 39b: 3.80 and 3.86 (each s, each OCH_3); 6.91 (d, J=1.8, CH); 7.44 (m, CH). The olefinic protons of isomer 38b are visible at 6.40 (s) and 6.88 (m).

38c / 39c = 1:4, bp. 100°/0.004 mm (short path distillation). IR ($CHCl_3$): 1725 (CO). ^{1}H-NMR ($CDCl_3$) of 39c: 3.77, 3.83 and 3.88 (each s, each OCH_3); 6.78 (d, J=2, H-C(2)); 7.97 (d, J=2, H-C(4)). The doublet (J=1.5) of isomer 38c is visible at 6.70 and 7.44.

6-Chloro-4-methoxycarbonyl-2H-pyran-2-one (40a). A solution of 38a / 39a (211 g, 0.88 mol), hydroquinone (0.8 g) and xylene (2 l) is refluxed for 26 hours. After evaporation the residue is extracted several times with hot hexane. The extracts are evaporated and the crystals thus obtained are sublimed (120°/0.1 mm): 134.2 g (81 %) 40a, mp. 51°. IR (KBr): 1755 (CO), 1715 (CO). ^{1}H-NMR ($CDCl_3$): 3.92 (s, OCH_3); 6.68 and 6.86 (each d, J=1.5, H-C(3) and H-C(5)).

4-Methoxycarbonyl-6-trifluormethyl-2H-pyran-2-one (40b). A mixture of 38b / 39b (210 g, 0.77 mol), hydroquinone (2g) and mesitylene (1 l) is refluxed for 70 hours. After evaporation, the residue obtained is distilled. The fractions between 65 and 75° (0.4 mm) are redistilled (60-64°/0.4 mm). Crystallisation with hexane/ether yields 92.4 g (62 %) 40b, mp. 38-40°. IR ($CHCl_3$): 1770 (CO), 1755 (CO). UV ($CHCl_3$): λ_{max}: = 303 (ε = 4100). ^{1}H-NMR ($CDCl_3$): 3.98 (s, OCH_3); 7.10 and 7.13 (each dq, each CH). ^{13}C-NMR ($CDCl_3$): 162.5 (COOMe); 158.3 (C(2)); 149.1 (C(6), J_{CF}=39); 142.5 (C(4)); 121.9 (C(3)); 117.8 (CF_3, J_{CF}=273); 103,1 (C(5), J_{CF}=4); 53.7 (OCH_3).

4,6-Dimethoxycarbonyl-2H-pyran-2-one (40c). Compound 38c / 39c (26.2 g, 0.1 mol) is refluxed in xylene for 24 hours. After evaporation the residue is distilled. The fraction between 135 and 145°/0.1 mm is crystallised from c-hexane: 2.35 g (12 %) 40c, mp. 99°. IR (KBr): 1760 (CO), 1725 (CO). ^{1}H-NMR ($CDCl_3$): 3.96 and 4.00 (each s, each OCH_3); 7.10 and 7.45 (each d, J=2, H-C(3) and H-C(5)).

4-Methoxycarbonyl-6-(2',6'-dichloropyridin-3'-yl)-2H-pyran-2-one (41). A mixture of dimethyl itaconate (31.6 g, 0.2 mol), 2,6-dichloro-3-trichloromethyl-pyridin[56] (53.0 g, 0.2 mol), CuCl (1 g, 0.01 mol) and 3-methoxypropionitrile is heated for 20 hours at 120°, then filtered and evaporated. The residue is treated with c-hexane and the precipitate is collected: 11.2 g (18 %) 41, mp. 157-159°. IR (KBr): 1770 (CO), 1740 (CO). ^{1}H-NMR ($CDCl_3$): 3.97 (s, OCH_3); 6.95 and 7.28 (each d, J=2, H-C(3)) and H-C(5)); 7.44 and 8.06 (each d, J=8, H-C(5') and H-C(4')).

6-Amino-4-methoxycarbonyl-2H-pyran-2-one (42). Aqueous NH_3 (25 %; 37.5 ml) is added dropwise to a solution of 40a (23.5 g, 0.125 mol) in ether (200 ml). After stirring for 1.5 hour the precipitate is collected, washed and dried: 15.1 g (71 %) 42 as a yellow powder, mp. 230° (dec.). IR (KBr): 3225 (NH_2), 3450 (NH), 1725 (CO), 1650 (CO). ^{1}H-NMR ($CDCl_3$): 3.82 (s, OCH_3); 5.57 and 5.61 (each d, J=1.5, H-C(3) and H-C(5)); 7.85 (broad s, NH_2, exch. with D_2O).

Trimethyl-1,2,3-prop-1-ene-tricarboxylate (43). To MeOH (70 ml) is added 40a (23.5 g, 0.125 mol) portionwise (temperature 60°). After 1 hour the solution is evaporated and the residue is distilled: 23.9 g (88 %) 43, bp. 140°/15 mm. IR (neat): 1725 (CO). ^{1}H-NMR ($CDCl_3$): 3.67, 3.74 and 3.80 (each s, each CH_3); 3.95 (s, CH_2); 6.93 (s, CH).

Cycloaddition of 40b with 1-pyrrolidino-1-cyclopentene. To a solution of 1-pyrrolidino-1-cyclopentene (1.46 g, 10.6 mmol) in THF (15 ml), compound 40b (2.35 g, 10.6 mmol) in THF (10 ml) is added dropwise. After stirring for 8 hours at 30° the solution is evaporated. The oily residue is chromatographed on silica gel (petrolether/ethylacetate 3:1): 3.52 g (92 %) 44, mp. 96-97°. IR ($CHCl_3$): 1795 (CO), 1788 (CO), 1740 (CO). ^{1}H-NMR ($CDCl_3$): 0.99 and 1.20 (each m, H_2-C(10)); 1.67 and 2.03 (each m, H_2-C(9) and H_2-C(11)); 1.75, 2.64 and 2.83 (each m, pyrrolidino-H); 3.06 (t, J=8, H-C(7)); 3.86 (s, OCH_3); 4.36 (d, J=2, H-C(4)); 7.36 (brd, J=2, H-C(6)). ^{13}C-NMR ($CDCl_3$): 168.4 (C(3)); 163.1 (CO-ester); 137.0 (C(5)); 135.5 (C(6)); 123.0 (CF_3, J_{CF}=280); 83.8 (C(1), J_{CF}=32); 73.0 (C(8)); 52.8 (OCH_3); 50.9 and 50.0 (C(4) and C(7)); 47.5 (CH_2-N); 29.3, 27.7 and 23.4 (remaining CH_2).

Cycloaddition of 40b with trimethylsilyloxy-cyclopent-1-ene. Compound 40b (7.0 g, 30 mmol), trimethylsilyloxy-cyclopent-1-ene (4.69 g, 30 mmol) and toluene (50 ml) are heated for 8 hours at 180° (autoclave). After evaporation the residue is chromatographed (silica gel, toluene). The main fraction is distilled (Kugelrohr: 100°/0.01 mm): 6.6 g (90 %) methyl 4-trifluoromethyl-6-indanate (45). IR ($CHCl_3$): 1720 (CO). ^{1}H-NMR ($CDCl_3$): 2.20 (m, H_2-C(2)); 3.00 and 3.12 (each t, H_2-C(1) and

H_2-C(3)); 3.92 (s, OCH_3); 8.04 and 8.10 (each brs, H-C(5) and H-C(7)).

Cycloaddition of 40b with tetramethoxyethylene. Tetramethoxyethylene (15.5 g, 0.1 mol) and 40b (5.5 g, 27 mmol) are heated for 50 hours at 100°. After evaporation the residue is purified by chromatography (silica gel; petrolether/ethylacetate 2:1): 10.7 g (73 %) 46, mp. 135-137°. IR ($CHCl_3$): 1979 (CO); 1735 (CO). ^{1}H-NMR ($CDCl_3$): 3.34 and 3.48 (each s, CH_3O-C(8)); 3.49 and 3.60 (each q, CH_3O-C(7)); 3.85 (OCH_3-ester); 4.36 (d, J=2.5, H-C(4)); 7.22 (d, J=2.5, H-C(6)). ^{13}C-NMR ($CDCl_3$): 165.3 (C(3)); 162.3 (CO-ester); 136.1 (C(6), J_{CF}=3); 132.2 (C(5)); 122.0 (CF_3, J_{CF}= 282); 104.1 (C(8)); 101.4 (C(7), J_{CF}=2); 83.9 (C(1), J_{CF}=31); 53.9 and 53.4 (CH_3O-C(7), J_{CF}=2 and 3); 52.8 (OCH_3-ester); 51.3 and 51.0 (CH_3O-C(8)); 49.5 (C(4)).

Cycloaddition of 40b with 3,4-dihydro-2H-pyrane. A solution of 40b (4.44 g, 20 mmol) in 3,4-dihydro-2H-pyrane (30 ml) is kept for 48 hours at 200° in an autoclave. After evaporation of the solution, the residue obtained is crystallized from c-hexane/toluene (2:1): 4.95 g (81 %) 47, mp. 130-132°. IR (KBr): 1795 (CO); 1730 (CO). ^{1}H-NMR ($CDCl_3$): 1.02, 1.56, 1.76 and 1.88 (each m, H_2-C(9) and H_2-C(10); 2.32 (m, H-C(8)), 3.64 and 3.83 (each m, H_2-C(11)); 3.86 (s, OCH_3); 4.01 (dd, J=3 and 2, H-C(4)); 4.25 (d, J=8, H-C(7)); 7.28 (d, J=2, H-C(6)). ^{13}C-NMR ($CDCl_3$): 168.1 (C(3), $J_{C(3),H-C(4)}$=4.5; $J_{C(3),H-C(8)}$=2.7, $J_{C(3),H-C(6)}$=1.5); 162.8 (CO-ester); 135.8 (C(5), $J_{C(5),H-C(8)}$=7); 134.1 (C(6)); 122.5 (CF_3, J_{CF}=281); 81.0 (C(1), J_{CF}=33); 72.9 (C(7)); 63.6 (C(11)); 52.8 (OCH_3); 44.6 (C(4)); 35.3 (C(8)); 20.5 and 20.2 (C(9) and C(10)).

Cycloaddition of 40b with 2,5-dihydrofurane. Compound 40b (4,4 g, 20 mmol) and 2,5-dihydrofurane (25 ml) are heated for 24 hours at 130°. The resulting solution is evaporated and the residue is crystallized (c-hexane/ethylacetate 1:1): 4.1 g (71 %) 48, mp. 92-94°. IR (KBr): 1790 (CO), 1725 (CO). ^{1}H-NMR ($CDCl_3$): 3.12 (m, H-C(8)); 3.40 (m, $J_{H-C(7),H-C(8)}$=9, H-C(7)); 3.57 and 3.82 (je m, H-C(9)); 3.68 and 3.74 (je m, H-C(11)); 3.87 (s, OCH_3); 4.20 (dd, $J_{H-C(4),H-C(8)}$=2.7, $J_{H-C(4),H-C(6)}$=1.9, H-C(4)); 7.31 (d, H-C(6)). ^{13}C-NMR ($CDCl_3$): 168.2 (C(3), $J_{C(3),H-C(4)}$=4.5, $J_{C(3),H-C(8)}$=$J_{C(3),H-C(6)}$=2); 162.8 (ester CO); 136.3 (C(5), $J_{C(5),H-C(8)}$=7.5); 134.1 (C(6)); 122.8 (CF_3, J_{CF}=280); 82.3 (C(1), J_{CF}=32); 70.6 (C(9)); 68.4 (C(11), J_{CF}=2); 53.0 (OCH_3); 46.3 (C(7)); 44.0 (C(4)); 40.5 (C(8)).

Cycloaddition of 40b with cyclopentene. A solution of 40b (11.0 g, 50 mmol) in cyclopentene (60 ml) is heated in an autoclave for 22 hours at 120°. After evaporation, the residue is chromatographed (silica gel, n-hexane, ethylacetate 4:1): 13.4 g (92 %) 49, bp 109°/0.1 mm. IR (neat): 1795 (CO), 1780 (CO) and 1735 (CO): ^{1}H-NMR ($CDCl_3$): 0.95 and 1.13 (je m, H-C(10)); 1.52, 1.77 and 2.00 (je m, H-C(9) and H-C(11)); 2.82 (m, $J_{H-C(8),H-C(4)}$=3, H-C(8)); 3.03 (m, H-C(7)); 3.88 (s, OCH_3), 4.13 (m, H-C(4)); 7.33 (d, $H_{H-C(4),H-C(6)}$=2, H-C(6)). ^{13}C-NMR ($CDCl_3$): 169.5 (C(3)); 162.9 (ester CO); 136.9 (C(5)); 135.5 (C(6)); 123.0 (CF_3, J_{CF}=280); 83.5 (C(1), J_{CF}=33); 52.8 (OCH_3); 45.6 (C(7)); 44.8 (C(4)); 40.3 (C(8)); 30.1 , 29.3 and 27.7 (CH_2).

Cycloaddition of 40b with cyclooctene. Compound 40b (13.31 g, 60 mmol) in cycloocetene (60 ml) is heated for 72 hours at 150° (autoclave). After evaporation, the residue obtained is distilled. The fraction between 135 and 150°/0.2 mm is chromatographed (silica gel, n-hexane/ethylacetate 5:1). The first fraction affords 9.4 g (47 %) 50. IR (neat): 1790 (CO), 1730 (CO). ^{1}H-NMR ($CDCl_3$): 1.1-1.9 (m, all CH_2); 2.83 (td, H-C(8)); 2.55 (t, H-C(7)); 3.84 (s, OCH_3); 4.00 (dd, J=3 and 2, H-C(4)); 7.25 (d, J=2, H-C(6)). The second fraction yields 5.7 g (43 %) of starting material 40b.

Cycloaddition of 40b with acenaphthylene. A mixture of 40b (4.0 g, 18 mmol), acenaphthylene (2.5 g, 16.4 mmol) and toluene (40 ml) is stirred for 30 hours at 100°. The precipitate is filtered off and washed with c-hexane: 5.5 g (89 %) 51, mp 206-208°. IR (KBr): 1790 (CO), 1735 (CO). ^{1}H-NMR ($CDCl_3$): 3.59 (s, OCH_3); 4.49 (dd, J=8 and 3, H-C(8)); 4.68 (d, J=8, H-C(7)); 4.78 (m, H-C(4)); 6.91 (d, J=2, H-C(6)); 7.3-7.7 (m, phenyl-H).

Cycloaddition of 40b with indene. A solution of 40b (6.6 g, 30 mmol) in indene (60 ml) is stirred 30 hours at 80°. The precipitate is collected and washed with c-hexane: 8.8 g (87 %) 52, mp 181-183°. IR (KBr): 1790 (CO), 1720 (CO). ^{1}H-NMR ($CDCl_3$): 2.59 (dd, J=17.5 and 5.5, H_{endo}-C(9)); 3.21 (dd, H=17.5 and 10.5, H_{exo}-C(9)); 3.44 (m, H-C(8)); 3.82 (s, OCH_3); 4.27 (d, J=8.7, H-C(7)); 4.35 (dd, J=3.5 and 2, H-C(4)); 7.11 (d, J=2, H-C(6)); 7.1-7.4 (m, phenyl-H).

Cycloaddition of 40b with vinylacetate. Compound 40b (6.66 g, 30 mmol) and vinylacetate (25 ml) are heated for 24 hours at 150° (autoclave). After evaporation the residue is chromatographed (silica gel, petrolether/ethylacetate 7:3). A first fraction yields 705 mg (11 %) 54. The main fraction affords 5.5 g (60 %) of all possible isomers of 53 (53a:53b:53c:53d = 13:57:3:27). IR ($CHCl_3$): 1795 (CO), 1750 (CO), 1730 (CO). ^{1}H-NMR ($CDCl_3$) of 53a: 1.52 (dt, J=14 and 3, H_{endo}-C(8)); 2.75 (ddd, J=14, 8 and 3, H_{exo}-C(8)); 4.15 (m, H-C(4)); 5.67 (dd, J=8 and 3, H-C(7)); 7.32 (d, J=2, H-C(6)). 53b: 1.84 (dd, J=15 and 2, H_{endo}-C(7)); 2.88 (dd, J=15 and 8, H_{exo}-C(7)); 4.52 (m, H-C(4)); 5.41 (brdt, H-C(8)); 7.41 (d, J=2, H-C(6)). 53c: 1.82 (H_{endo}-C(8)); 2.39 (H_{exo}-C(8)); 5.32 (dd, J=8 and 3, H-C(7)); 7.20 (d, J=2, H-C(6)): 53d: 2.18 (dd, J=15 and 3, H_{exo}-C(7)); 2.49 (dd, J=15 and 9, H_{endo}-C(7)); 4.35 (m, H-C(4)); 5.07 (dt, J=9 and 3, H-C(8)); 7.39 (d, J=2, H-C(6)). ^{13}C-NMR ($CDCl_3$), inter alia: 167.7 (C(3) of 53a); 166.23 (C(3) of 53d), $J_{C(3),H-C(4)}$=3.8, $J_{C(3),H-C(8)}$=8.2, $J_{C(3),H-C(6)}$=1.5); 166.16 (C(3) of 53b, $J_{C(3),H-C(4)}$=5.0, $J_{C(3),H-C(8)}$=$J_{C(3),H-C(6)}$=1.2; 138.9 (C(5) of 53d); 137.5 (C(6) of 53d); 135.1 (C(5) of 53b); 134.7 (C(6) of 53b); 133.0 (C(6) of 53a). Digital resolution of the proton coupled spectrums: 0.15 Hz.

Cycloaddition of 40b with norbornadiene. Compound 40b (88 g, 0.4 mol) and norbornadiene (480 ml) are heated in an autoclave for 24 hours at 150°. The mixture is then evaporated and the residue is distilled: 70.9 g (87 %) methyl-3-trifluoromethyl-benzoate 54, bp. 76°/17 mm). IR ($CHCl_3$): 1730 (CO). ^{1}H-NMR ($CDCl_3$): 3.92 (s, CH_3); 7.58 brt, H-C(5)); 7.82 (brd, H-C(4)); 8.23 (brd, H-C(6)); 8.31 (brs, H-C(2)).

Cycloaddition of 40b with acetylene. A solution of 40b (10.0 g, 45 mmol) in toluene (100 ml) is put in an autoclave. Acetylene is injected (16 bar). The autoclave is heated for 24 hours at 200° with addition of further acetylene to maintain a pressure of 20 bar. After cooling, distillation yields 8.3 g (91 %) 54, bp. 75-77°/18 mm.

Cycloaddition of 40b with 1-diethylamino-1-propine. To the solution of 40b (22.2 g, 0.1 mol) in toluene (40 ml) is added at 0° dropwise 1-diethylamino-1-propin (12.5 g, 0.12 mol) in toluene (20 ml). Vigorous evolution of CO_2 is observed. After stirring for 15 min. at 0°, the reaction mixture is evaporated and the residue distilled: 19.8 g (68 %) N,N-diethyl-2-trifluoromethyl-4-methoxycarbonyl-6-methyl-aniline (55), bp. 91-92°/0.3 mm. IR (neat): 1725 (CO). ^{1}H-NMR ($CDCl_3$): 1.04 (t, J=7, CH_3); 2.37 (s, CH_3-C(6)); 3.12 (br, CH_2-N); 3.92 (s, OCH_3); 7.99 (d, J=2, H-C(3)); 8.15 (d, J=2, H-C(5)). ^{13}C-NMR ($CDCl_3$): 166.1 (CO); 153.2 (C(1)); 140.9 (C(6)); 136.1 (C(5)); 131.3 (C(2), J_{CF}=28); 126.7 (C(4)); 126.6 (C(3), J_{CF}=7); 123.9 (CF_3, J_{CF}=274); 52.3 (OCH_3); 47.5 (CH_2N); 19.6 (CH_3-C(6)); 14.0 (CH_3-CH_2).

Cycloaddition of 40b with phenylacetylene. A solution of 40b (16.89 g, 76 mmol) and phenylacetylene (23.25 g, 0.23 mol) in toluene (80 ml) is kept for 9 hours at 180° in an autoclave. After evaporation of the solvent, the residue is distilled: 8.3 g (39 %) of a 60:40-mixture of the isomers 56 and 57, bp 150°/0.01 mm. IR ($CHCl_3$): 1735 (CO). ^{1}H-NMR ($CDCl_3$): 4.00 (s, OCH_3); 7.3-7.7 (m, phenyl-H); 8.22 (dd, H-C(5) of 56); 8.43 (d, H-C(3) of 56); 8.01, 8.28 and 8.46 (each sbr, H-C(2), H-C(6) and H-C(4) of 57).

Cycloaddition of 40b with dimethylacetylenedicarboxylate. A mixture of 40b (4.8 g, 21.6 mmol) and dimethylacetylenedicarboxylate (3.96 g, 28 mmol) is kept for 20 hours at 180° in an autoclave. The resulting viscous oil is distilled. The fraction between 80 and 95°/0.01 mm is collected and crystallized (ether/n-hexane): 3.4 g (67 %) 3-trifluoromethyl-1,2,5-trimethoxycarbonylbenzene (58), mp 47-49°. IR (KBr): 1755 (CO) and 1735 (CO). ^{1}H-NMR ($CDCl_3$): 3.96, 4.00 and 4.01 (each s, each OCH_3); 8.54 (dbr, H-C(4)); 8.85 (dbr, H-C(6)). ^{13}C-NMR ($CDCl_3$): 166.4, 164.3 and 164.2 (each CO); 137.2 (C(2), J_{CF}=2); 134.5 (C(6)); 131.8 (C(5)); 131.2 (C(4), J_{CF}=5); 130.0 (C(1)); 129.2 (C(3), J_{CF}=33); 122.5 (CF_3, J_{CF}=275); 53.4, 53.2 and 53.0 (each CH_3).

Cycloadition of 40b with p-chlorophenyl-chloroacetylene. A solution of 40b (21.0 g, 94 mmol) and p-chlorophenyl-chloroacetylene (32.8 g, 109 mmol) in xylene (60 ml) is refluxed for 36 hours, then evaporated. The residue is crystallized from ether: 31.6 g (70 %) 60, mp. 195-197°. IR ($CHCl_3$): 1800 (CO); 1750 (CO); 1735 (CO). ^{1}H-NMR ($CDCl_3$): 3.77 (s, OCH_3); 4.86 (d, J=2, H-C(4)); 7.25 (d, J=2, H-C(6)); 7.32, 7.35 and 7.41, 7.45 (each AA'BB', phenyl-H).

2,2,4-Trichloro-4-methoxycarbonyl-butyric acid chloride (64a). A mixture of methyl acrylate (430.5 g, 5 mol), trichloroacetic acid chloride (909 g, 5 mol), acetonitrile (2 l) and CuCl (32 g, 0.32 mol) is heated in an enamel autoclave at 115° for 24 hours. The cooled reaction mixture is evaporated, copper salts are removed by filtration and the oil is distilled: 918.5 g, (69 %) 64a, bp. 66-68°/0.01 mm. IR ($CHCl_3$): 1750 (CO). ^{1}H-NMR ($CDCl_3$): 3.19 (m, J=15 and 5, H-C(3)); 3.42 (m, J=15 and 7, H-C(3)); 3.82 (s, OCH_3); 4.64 (m, J=5 and 7, H-C(4)).

2,2,4-Trichloro-4-methoxycarbonyl-pentanecarboxylic acid chloride (64b). Methyl methacrylate (200.4 g, 2 mol), trichloro-acetyl chloride (545.4 g, 3 mol), acetonitrile (800 ml) and CuCl (12 g, 0.12 mol) are heated as described above. Distillation affords 329.8 g (59 %) 64b, bp. 87-90°/0.2 mm. IR ($CHCl_3$): 1800 (CO), 1740 (CO). ^{1}H-NMR ($CDCl_3$): 1.88 (s, CH_3); 3.52 and 3.63 (AB, J=15, H_2-C(3)); 3.85 (s, OCH_3).

2,4-Dichloro-4-methoxycarbonyl-butyric acid chloride (64c). Dichloroacetyl chloride (600 g, 4 mol), methyl acrylate (172 g, 2 mol), acetonitrile (400 ml) and CuCl (12 g, 0.12 mol) are heated as described for the preparation of 64a. Distillation yields 145.7 g (32 %) 64c, bp. 60-62°/0.03 mm. IR ($CHCl_3$): 1795 (CO), 1750 (CO). ^{1}HNMR ($CDCl_3$): 2.45-3.6 (m, 3H); 3.84 (s, OCH_3); 4.4-4.95 (m, 1H).

General procedure for the preparation of 66. To a solution of the amine (0.5 mol) in toluene (500 ml) is added dropwise 64a (0.5 mol) in toluene (500 ml), and then triethylamine (1 mol) in toluene (450 ml). The reaction mixture is heated at 60° for 6 hours and, after cooling, is acidified with 1N HCl. The organic layer is washed with H_2O, dried over $MgSO_4$ and evaporated. The residue is crystallized from ether/n-hexane or distilled. Yields and mps: see table 3. In ^{1}H-NMR spectra all compounds show an ABX-system with J_{AB}=14-15, J_{AX}=7-8 and J_{BX}=3-7 Hz. For illustration two ^{1}H-NMR spectra are

given as follows ($CDCl_3$): 66m: 1.31 (d, J=7, CH_3); 1.38 (d, J=7, CH_3); 3.01 (m, J=15 and 5, H-C(4)); 3.20 (m, J=15 and 7, H-C(4)); 3.80 (s, OCH_3); 4.0 (m, J=7, CH); 4.29 (m, J=5 and 7, H-C(5)). 66n: 1.30 (t, J=7, CH_3); 3.02 (m, J=14 and 6, H-C(4)); 3.31 (m, J=14 and 8, H-C(4)); 3.82 (s, OCH_3); 4.21 (q, J=7, CH_2O); 4.53 (m, J=6 and 8, H-C(5)); 7.35 (sb, NH).

Lactone of 2,2-dichloro-4-hydroxy-4-methoxycarbonyl-butyric acid (67). To a solution of 64a (53.6 g, 0.2 mol) in acetonitrile (80 ml) is added dropwise H_2O (3.93 g, 0.22 mol) in acetonitrile (30 ml); the temperature increases to 55°. After cooling, the mixture is filtered and the filtrate is evaporated. The residue is distilled: 37.9 g (88 %) 67, bp. 103-105°/0.1 mm. IR (neat): 1815 (CO), 1750 (CO). ^{1}H-NMR ($CDCl_3$): 3.17 and 3.42 (AB of ABX , J_{AB}=14, J_{AX}=J_{BX}=7, H_2-C(3)); 3.87 (s, OCH_3); 5.05 (X of ABX, J_{AX}=J_{BX}=7, H-C(4)).

3-Chloro-1-(2,6-dimethylphenyl)-5-methoxycarbonyl-2-oxo-pyrrolidine (68). A mixture of 66e (31.8 g, 0.1 mol), granulated zinc (65 g, 1 mol) and acetic acid (220 ml) is stirred at 10° for 7 hours until 66e completely disappears. The reaction mixture is filtered. The filtrate is poured into icewater, the precipitate is collected, washed with H_2O and dried. Chromatography (toluene-ethylacetate 4:1) of the crude material yields the two isomeres 68a (9.3 g, 33 %) and 68b (8.7 g, 31 %) and the fully dechlorinated 68 (4.2 g, 17 %). 68a: mp. 89-90°. IR (KBr): 1755 (CO), 1705 (CO). ^{1}H-NMR ($CDCl_3$): 2.22 (s, CH_3); 2.26 (s, CH_3); 2.5-3.0 (m, 2H); 3.58 (s, OCH_3); 4.55-4.80 (m, 2H); 7.08 (m, 3H). 68b: mp. 115-116°. IR (KBr): 1760 (CO), 1710 (CO). ^{1}H-NMR ($CDCl_3$): 2,17 (s, CH_3); 2.36 (s, CH_3); 2.7 (m, 1H); 3.05 (m, 1H); 3.61 (s, OCH_3); 4.53-4.57 (m, 2H); 7.1 (m, 3H). Fully dechlorinated 68: mp. 87-88°. IR (KBr): 1755 (CO), 1705 (CO). ^{1}H-NMR ($CDCl_3$): 2.22 (s, CH_3); 2.27 (s, CH_3); 2.4-2.9 (m, 4H); 3.62 (s, OCH_3); 4.48 (m, 1H); 7.07 (m, 3H).

2-Methoxycarbonyl-1-(3-trifluoromethylphenyl)-pyrrolidine (71). a) Dechlorination of 66b: as above for 68, but with Zn-powder and at 60°, gives 70 in 97 % yield, mp. 64-65°. b) Reduction of the amide 70: To a solution of 70 (28.7 g, 0.1 mol) in CH_2Cl_2 (140 ml) is added triethyloxonium tetrafluoroborate (19 g, 0.1 mol). The reaction mixture is stirred for 20 hours at 22°, then evaporated. The residue is dissolved in ethanol (350 ml) and at 0°, $NaBH_4$ (18.9 g, 0.5 mol) is added in portions during 2 hours. The reaction mixture is then stirred for 14 hours at 20°, poured into water and extracted with ether. The extract is washed with water, dried ($MgSO_4$) and evaporated. Distillation of the residue affords 13.3 g (49 %) 71, bp. 115-117°/0.04 mm. IR (neat): 1740 (CO). ^{1}H-NHR ($CDCl_3$): 1.95-2.35 (m, 4H); 3.2-3.6 (m, 2H); 3.70 (s, OCH_3); 4.25 (m, H-C(2)); 6.55-7.30 (m, 4H).

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