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Heterocycle construction using the biomass-derived building block itaconic acid

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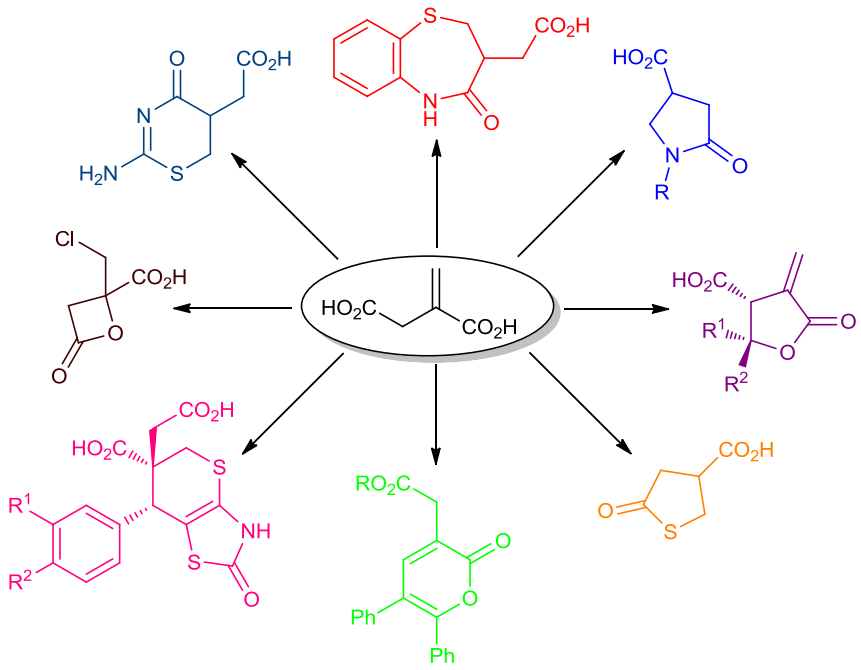

Abstract

This critical review discusses the diverse array of heterocyclic motifs that are available from the biomass-derived building block itaconic acid.

1. Introduction

2. Five-Membered Heterocycles

2.1 Nitrogen

2.2 Oxygen and Sulfur

2.3 Cycloadditions

3. Six-Membered Heterocycles

1. Introduction

A major recommendation within the vision 2020 catalysis report is the improved use of renewable feedstocks (biomass) in the production of valuable chemicals.[1] As an enormous amount of society-enhancing chemicals are reliant on synthetic chemistry for their production, employing substrates obtained from renewable sources in the synthesis of these aforementioned compounds will secure their supply at the levels we enjoy access to today.

Heterocycles (cyclic molecules where one or more carbon atoms are replaced with a heteroatom - typically nitrogen, oxygen or sulfur) account for over half of all known organic compounds. Many classes of natural products, a large majority of commercially important drugs, agrochemicals, functional materials, dyes etc all contain heterocyclic rings. As such, the development of heterocycle syntheses that involve compounds attainable from biomass will likely have positive implications in the future production of the aforementioned value-added products. This review showcases the broad range of heterocyclic motifs that are available from itaconic acid (**1**, Figure 1), a fully sustainable, non-toxic, five carbon chemical building block that features on the U.S. DOE National Renewable Energy Laboratory's Top 12 list of renewable chemicals attainable from biomass.[3] The vast majority of syntheses described herein are either single-step or one-pot processes, but selected others have been included for completeness. For efficiency reasons, synthetic routes that require an initial reduction of (**1**) to the corresponding diol are not included.

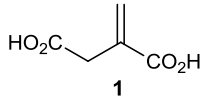

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Figure 1. Itaconic acid

Itaconic acid was first discovered by Baup in 1837 as a product from the thermal decomposition of citric acid.[4] It was not until 1932 that itaconic acid was isolated from the fungal strain *Aspergillus itaconicus*.[4,5] The production of itaconic acid using biosynthetic

processes currently relies on *Aspergillus terreus*, specifically strain NRRL1960 due to its superior production volumes of up to 80-90g/L.[4,6] Optimizing the aerobic fungal fermentation is still required in order to reach the theoretical maximum of 240g/L.[7] The final step in biosynthesis of itaconic acid involves the C5-decarboxylation of *cis*-aconitate, which is simultaneously produced with citrate as part of the citric acid cycle.[6-8]

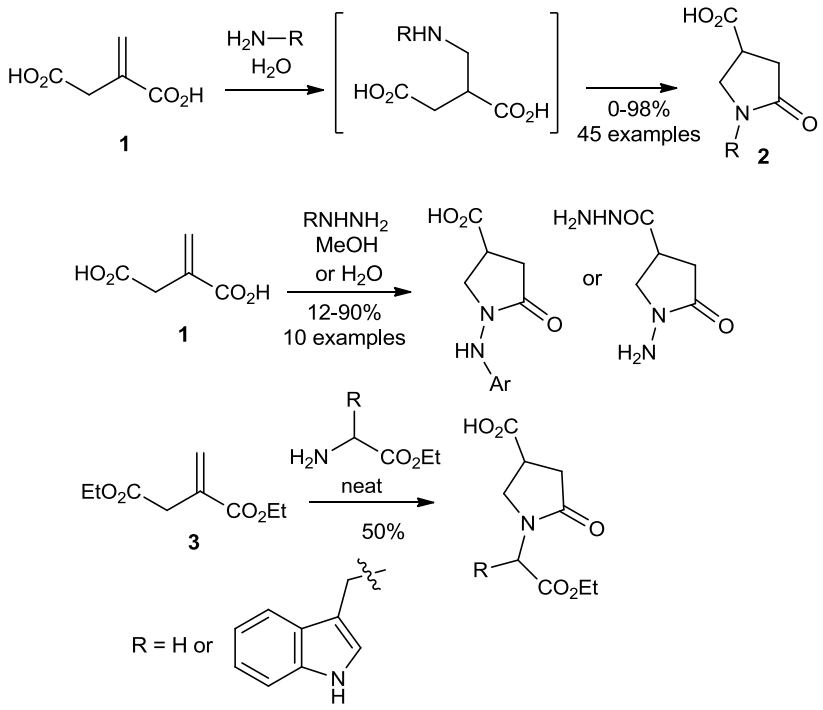
The estimated production volume of itaconic acid from 2009-2013 has been estimated at between 40 and 80kt/annum.[6a,6b,9] The production costs have halved from around $US4.00/kg[6a] in 2001 to around $US2.00/kg in 2013.[6b] Greater than 25% of the production costs are dictated by the carbon source employed in the fermentation.[6b] An attractive source is xylose, a readily obtainable, renewable feedstock from hardwood and agricultural residues.[9] However, current yields of itaconic acid obtained from 5-carbon sugars such as xylose are not as great as those obtained from the fermentation of 6-carbon sugars.[10] However, employing glucose in this process, primarily in the form of molasses from sugar cane or beets, is more expensive.[6b,11] Presently, the primary uses for itaconic acid include applications in plastics, rubbers, as a co-monomer in resins, the detergent industry as a surface active agent and the textile industry. Itaconic acid can also be used in the production of green plastics which are not harmful to health or the environment.[7] The predicted market for itaconic acid for 2020 is 200kt, but if itaconic acid can be successfully incorporated into the production of methyl methacrylate (MMA; used in acrylic glass production) this demand will more than double to 414kt.[9] Furthermore, a detailed evaluation of chemicals that could potentially be replaced with itaconic acid increases its total addressable market volume to 6163kt/annum.[9]

2. Five-Membered Heterocycles

2.1 Nitrogen

The observation that primary amines react with itaconic acid to produce 4-carboxy-2-pyrrolidones has been known since the mid-late 1800's,[12] but it wasn't until 1950 that a detailed evaluation of this reaction was conducted.[13] Over forty amines and anilines underwent condensation with itaconic acid, affording a series of *N*-substituted-4-carboxy-2-pyrrolidones (**2**). A short time later, it was demonstrated hydrazines underwent an analogous reaction with **1** to give *N*-amino pyrrolidones[14] and that amino-acids were viable substrates when condensed with diethyl itaconate (**3**)[15] (Scheme 1). This heterocycle synthesis employs environmentally favourable solvents, is compatible with various nitrogen nucleophiles and is

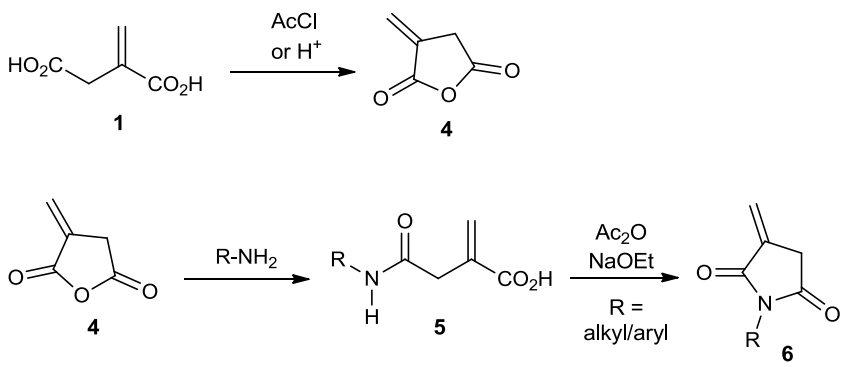
thus a popular method to construct 2-pyrrolidones for use in a wide range of applications.[16] It can be envisaged that these biomass-derived routes may have implications in the synthesis of 2-pyrrolidone based value-added products such as polyvinylpyrrolidone (PVP)[17] a versatile synthetic biocompatible polymer,[18] several pharmaceutials[19] and in the production of the increasingly popular biodegradable solvent *N*-methylpyrrolidone.[20]



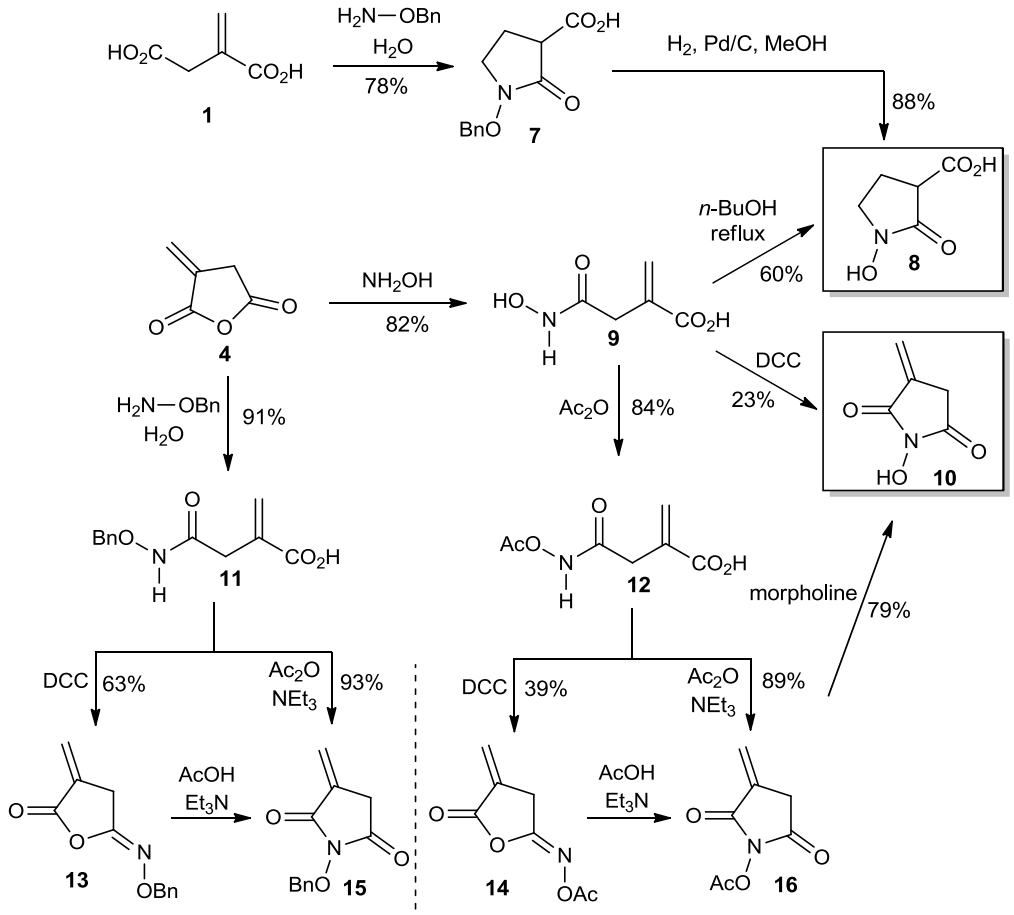
Scheme 1

The cyclodehydration of itaconic acid (**1**) affords itaconic anhydride (**4**),[21] a 3-methylene succinic anhydride that could potentially be useful in the synthesis of alkenyl succinic anhydrides (ASAs), compounds currently obtained from petrochemical sources with important roles as corrosion inhibitors, plasticizers and additives for engine oil and moisture control.[22] Importantly, itaconic anhydride has many interesting synthetic applications that often contrast those of itaconic acid. For example, in a process that provides structurally distinct products to the chemistry outlined in Scheme 1, itaconic anhydride (**4**) undergoes regioselective ring-opening with amines, giving amides **5** which upon lactamization affords succinimides **6** (Scheme 2),[23] important heterocycles present in many pharmaceuticals and agrochemicals, including the anticonvulsants ethosuximide, phensuximide, methsuximide[24] and the non-carcinogenic fungicide captan.[25]

Akiyama has extended this chemistry to the synthesis of several interesting heterocyclic motifs (Scheme 3).[26] The reaction of itaconic acid **1** with *O*-benzylhydroxylamine gives the 1-benzyloxypyrrolidone **7** which upon hydrogenolysis, delivers the 1-hydroxypyrrolidone **8**. The same heterocycle **8** can be accessed by the ring opening of **4** with hydroxylamine followed by an intramolecular conjugate addition of the resulting hydroxyamide **9**. Interestingly, the same intermediate **9** undergoes lactamization upon exposure to DCC, forming the *N*-hydroxyimide **10**. More functionally diverse heterocycles are available using the same intermediates already mentioned above; for example, the reaction of **4** with *O*-benzylhydroxylamine gives **11**, with the analogous acetate **12** readily available from **9**. Treatment of **11** and **12** with DCC gave the isoimides **13** and **14**, whereas exposing the same compounds to acetic anhydride and triethylamine delivered the benzyloxyimide **15** and acetoxyimide **16** respectively. The rearrangement of isoimides **13** and **14** to imides **15** and **16** is readily promoted with acetic acid-triethylamine. Aminolysis of **16** with morpholine provides a complementary route to **10**.

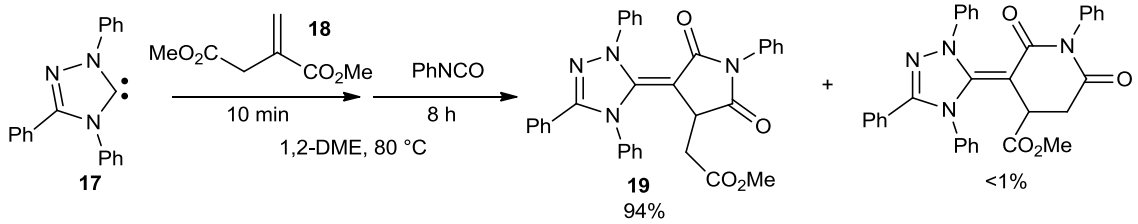


Scheme 2



Scheme 3

Itaconic acid derivatives are often employed as substrates during synthetic methodology studies, resulting in quite unique heterocyclic motifs. A good example is the three component coupling between the *N*-heterocyclic carbene **17**, phenylisocyanate and dimethyl itaconate (**18**) that proceeds in near perfect regioselectivity to give the imide **19** in excellent yield (Scheme 4).[27]

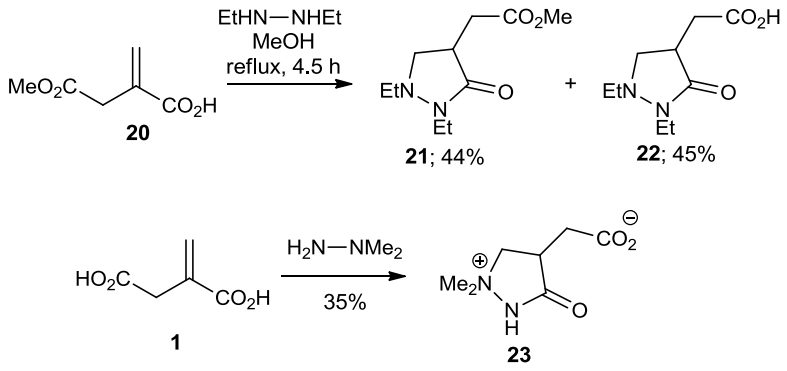


Scheme 4

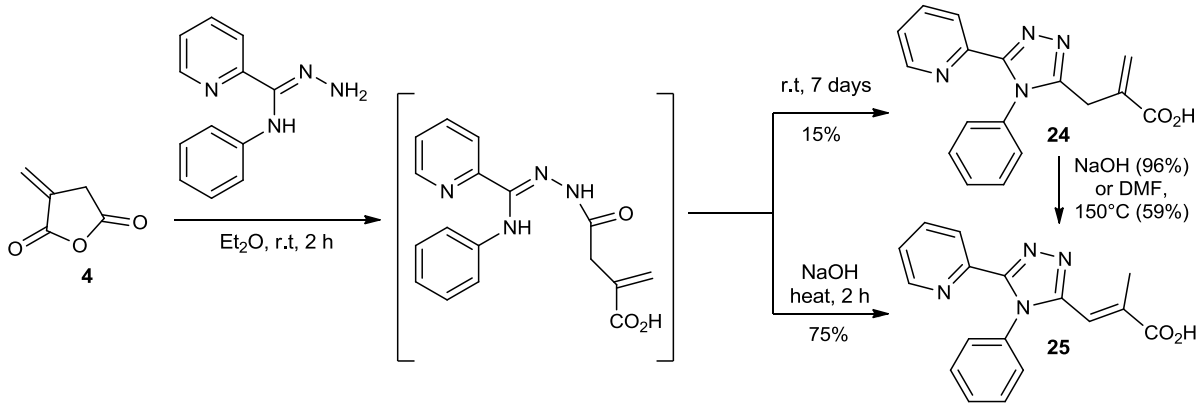
Heterocycles containing more than one heteroatom can be accessed from itaconic acid derivatives. The reaction of 1,2-diethylhydrazine with 4-methylitaconate (**20**) proceeds in excellent yield to give the pyrazolidone **21**, along with its hydrolysis product **22**.[28] Similarly,

itaconic acid (**1**) reacts with 1,1-dimethylhydrazine to give the heterocycle **23** (Scheme 4).[29] This approach to pyrazolidones could have implications in the synthesis of related pyrazoles, a key heterocyclic subunit of the nonsteroidal anti-inflammatory drug (NSAID) celebrex, the blockbuster viagra[30] and the antidepressant zomatepine.[31]

An interesting triazole synthesis involving itaconic anhydride has been reported. Depending on the reaction conditions, the 1,2,4-triazoles **24** and **25** can be selectively obtained from the reaction of *N*-phenyl-(pyridine-2-yl)carbohydrazonamide with itaconic anhydride (**4**) (Scheme 5).[32] 1,2,4-Triazoles are important heterocyclic motifs[33] perhaps best known for their presence in the anti-fungals fluconazole[34] and itraconazole,[35] but can also be found in other medicinally important compounds including analgesics.[33a,35] This motif has also been investigated in functional coordination polymer gels (CPG's), a class of compounds with a variety of applications and properties including physical stimuli response, redox responsiveness, catalysis, and phosphorescent behaviour.[36] Interestingly, there are few synthetic routes that provide densely substituted 1,2,4-triazoles such as those seen in Scheme 5.[37]



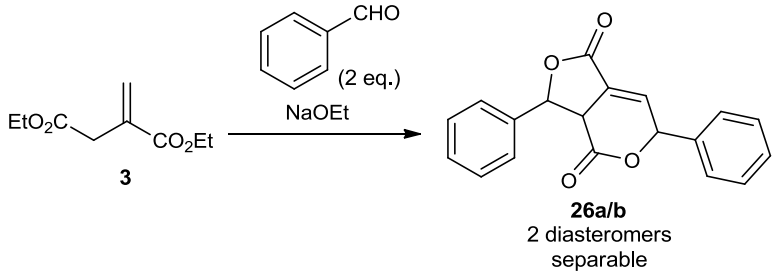
Scheme 4



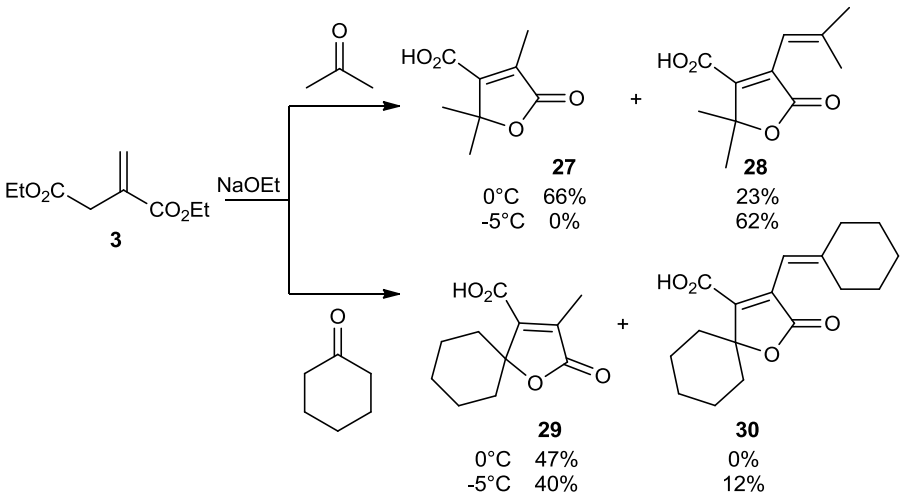
Scheme 5

2.2 Oxygen and Sulfur

At the beginning of the 20th century, Fittig examined the reactivity of the active methylene group in diethyl itaconate (**3**).[38] Under basic conditions, condensation of **3** with benzaldehyde gave a diastereomeric mixture of diphenylheptenedilactone and isodiphenylheptenedilactone **a/b** favouring the former (Scheme 7). Katsuda later showed that the base promoted reaction of diethyl itaconate (**3**) with acetone gave the aconic acids **27** and **28**, the latter arising from a second condensation with acetone (Scheme 8).[39] Although **27** was the major product at 0 °C, **28** was exclusively formed when the reaction was run in an ice-bath. Interestingly, when the same reaction was repeated with cyclohexanone, only the lactone **29** was formed at 0 °C, with a small amount of the product **30** appearing at the lower temperature. The potential of the methodology outlined in Scheme 8 is huge, as the butenolide motif is features heavily in several classes of natural compounds.[40]

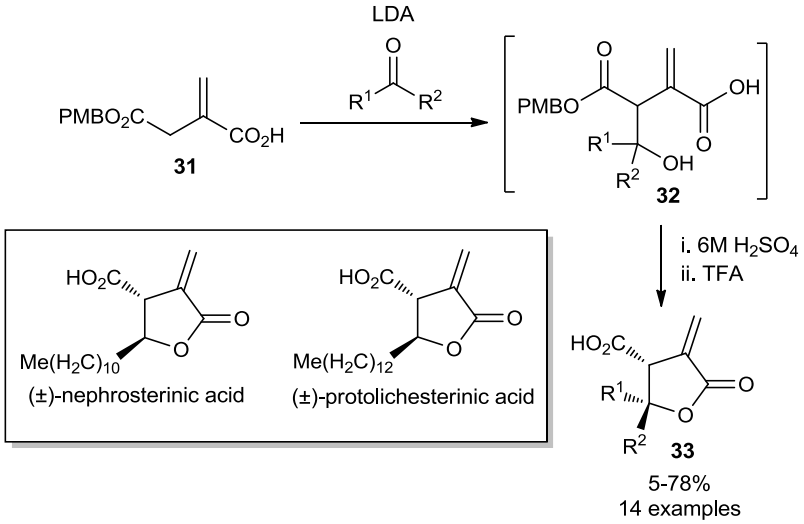


Scheme 7



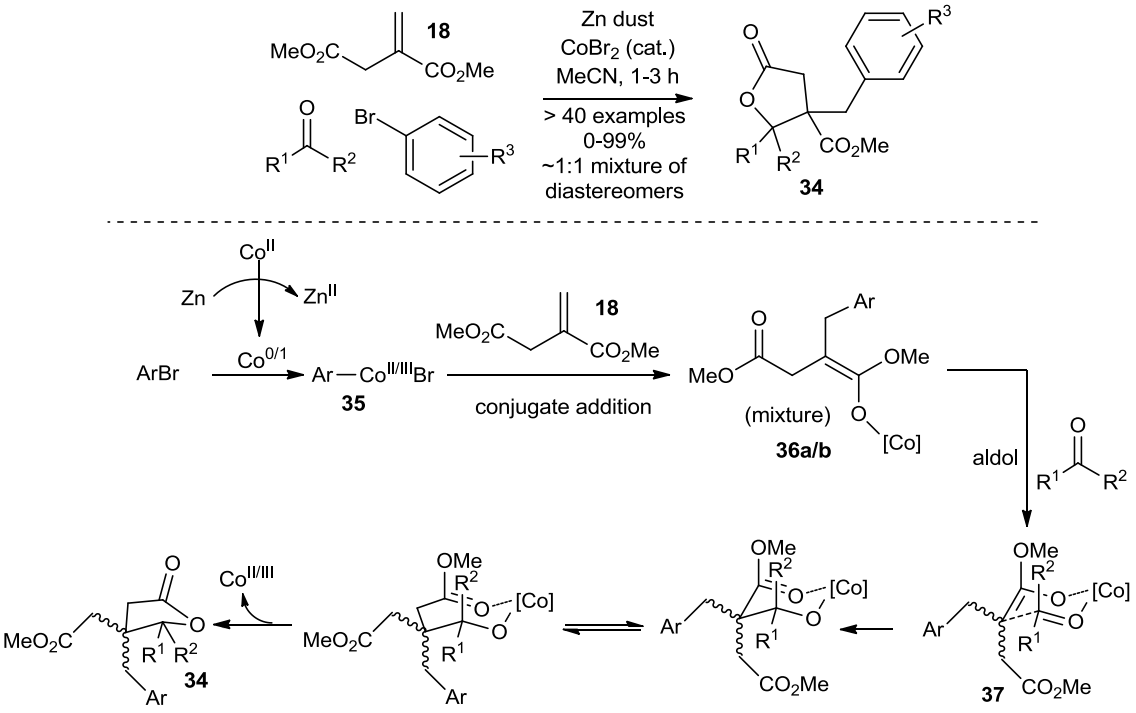
Scheme 8

Carlson has demonstrated that the dianion derived from 4-*para*-methoxybenzyl itaconate (**31**) can add to aldehydes and ketones, forming intermediates **32** that upon lactonization (H_2SO_4) and PMB removal (TFA), deliver a series of α-methylene-γ-butyrolactones **33** including the natural products (±)-nephrosterinic acid and (±)-protolichesterinic acid (Scheme 9).[41] This methodology has been used during the synthesis of α-methylene-γ-butyrolactones for evaluation as antimycobacterial agents[42] and small molecule inhibitors of histone acetyltransferase (HAT) Gcn5.[43] When considering the potential applications of this methodology, it is worth noting that α-methylene-γ-butyrolactones have been estimated to feature in around 10% of all known natural products.[44]



Scheme 9

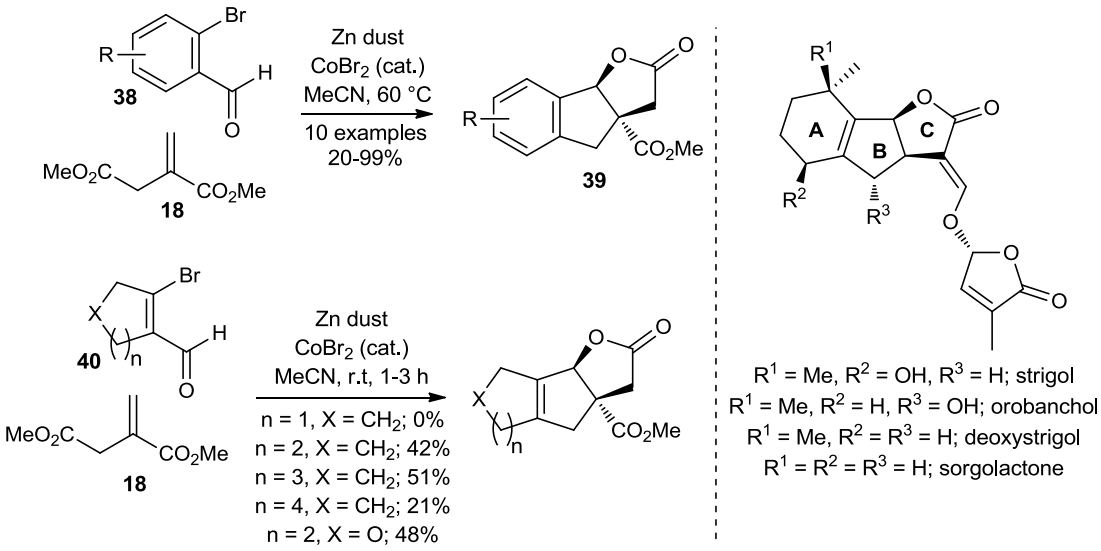
A three-component synthesis of densely functionalised γ-butyrolactones (**34**) using dimethyl itaconate (**18**), arylbromides and carbonyl compounds has been achieved (Scheme 10).[45] This Barbier-type process proceeds through a metalation-conjugate addition-aldol-lactonization reaction sequence, tolerating a vast array of substituents on the arylbromide component, and is compatible with a variety of (hetero)arylaldehydes and ketones. This methodology has been used to synthesise novel paraconic acid analogues for cytotoxic evaluation.[46] It is proposed the reaction commences with formation of the organocobalt species **35** which undergoes conjugate addition to **18** to give a mixture of cobalt enolates **36a** and **36b**. Aldol reaction followed by lactonization delivers the products **34**.[45b] Upon examining the Zimmerman-Traxler transition state (**37**) for the aldol reaction, clear evidence for poor diastereoselectivity for the overall reaction is obtained, as the similar steric hindrance between $–CH_2Ar$ and $–CH_2CO_2Me$ does not permit a notable predominance for either the *Z*- or *E*-enolate.



Scheme 10

In a related study, the same authors discovered that by combining the aldehyde and aryl bromide components in the aforementioned three-component coupling, *ortho*-bromobenzaldehydes **38** and dimethyl itaconate (**18**) successfully underwent a cobalt-catalysed domino reaction to furnish fused tricyclic cyclopent[*b*]furan-2-ones **39** analogous to

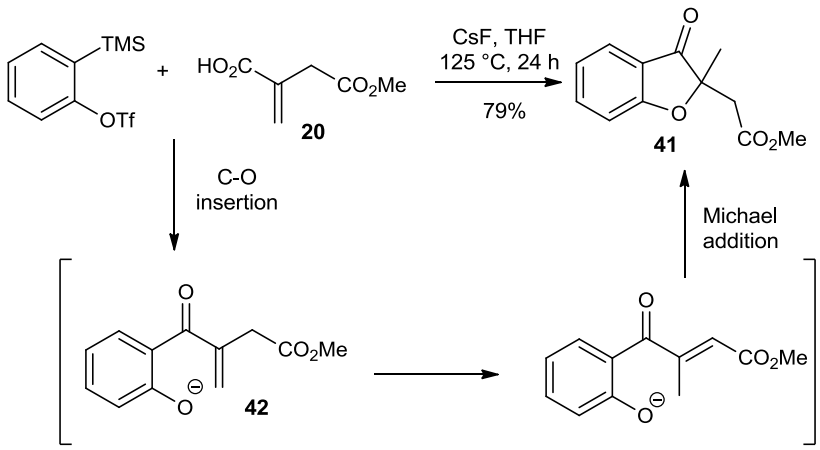
the ABC tricyclic core of the strigolactone family of plant hormones. α-Bromoenals **40** show varying levels of success in this process (Scheme 11).[47]



Scheme 11

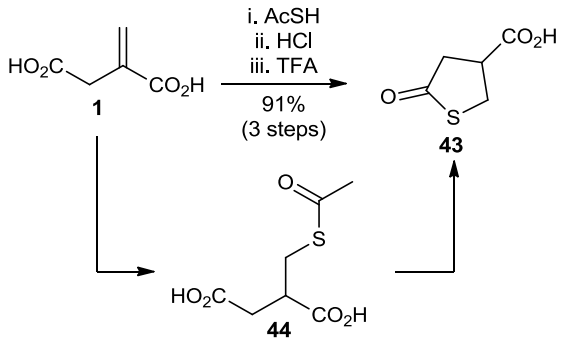
Sustainable syntheses of γ-butyrolactones (the products observed in schemes 9-11) are important for a variety of reasons. For example, 2-acetyl-γ-butyrolactone is utilized in the synthesis vitamin B1.[48] γ - Butyrolactones have served as key intermediates in the synthesis of several natural products[49] and the glaucoma treatment pilocarpine features a γ-butyrolactone moiety.[50] γ-Butyrolactones are excellent lead structures for new novel antibiotics due to the existence of microbial species specific γ - butyrolactone receptors that as transcriptional regulators, are associated with antibiotic resistance.[51] In addition, poly(γ-butyrolactones) have potential application as tissue scaffolds.[52]

Under relatively forcing conditions, 4-methylitaconate (**20**) reacts with benzyne to give coumaranone **41** (Scheme 12).[53] The reaction proceeds by an interesting C–O insertion into benzyne to give **42** which upon isomerization and conjugate addition affords the product **41**, a heterocyclic motif that is not readily accessible using other methods. This synthetic methodology is significant as 3-coumaranones (benzofuran-3-ones) are present in the aurone class of flavonoids,[54] isolable from some flowers, vegetables and marine sponges[54,55] and griseofulvin - isolated from filamentous fungi.[56] Several aurones and griseofulvin have many promising medicinal applications.[54,56b.]



Scheme 12

Carboxythiolactone **43** is available by the conjugate addition of thioacetic acid to itaconic acid followed by acid-mediated cyclization of **44** (Scheme 13).[57] Recently, it was shown that after controlled copolymerization of a thiolactone monomer, aminolysis of the resulting poly(thiolactone) yields a linear polythiol scaffold upon which thiol-click modification processes can be conducted.[58] This process allows for metal free post-polymerisation modifications to be performed under relatively straightforward conditions, providing an excellent alternative to commonly employed alkyne-azide click cycloaddition processes.[58b]



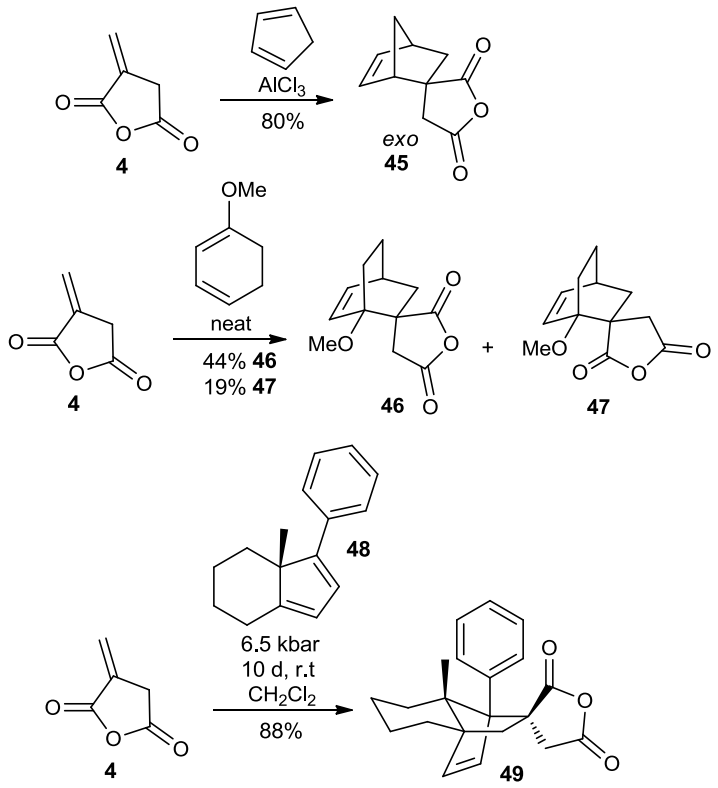
Scheme 13

2.3 Cycloadditions

The C=C bond present in itaconic anhydride (**4**) provides an excellent handle upon which to conduct cycloaddition reactions. Indeed, itaconic anhydride (**4**) undergoes many [4+2]- and

dipolar-cycloaddition processes, providing access to heterocyclic motifs containing oxygen and/or nitrogen. For the purposes of clarity, all the cycloaddition chemistry involving **4** (and itaconic acid derivatives) as the dienophile/dipolarophile is compiled in the following section.

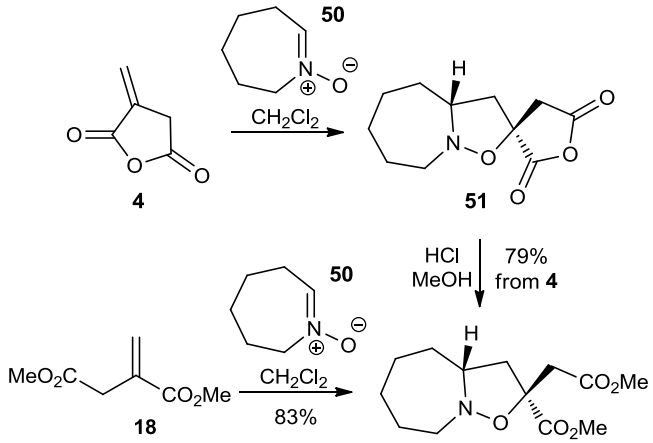
In their landmark paper, Diels and Alder showed that **4** reacts with cyclopentadiene to give the *exo*-cycloadduct **45**.[59] 1-Methoxycyclohexadiene also works well in this process, giving a 2.3:1 mixture of *exo*- and *endo*-diastereomers **46** and **47**.[60] The room temperature, high pressure cycloaddition between **4** and homochiral cyclopentadiene **48** gives **49** as a single diastereomer.[61] Interestingly, the cycloadduct **49** undergoes slow cycloreversion at room temperature, a process that can only be halted upon crystallization and storage at cold temperatures (Scheme 14).



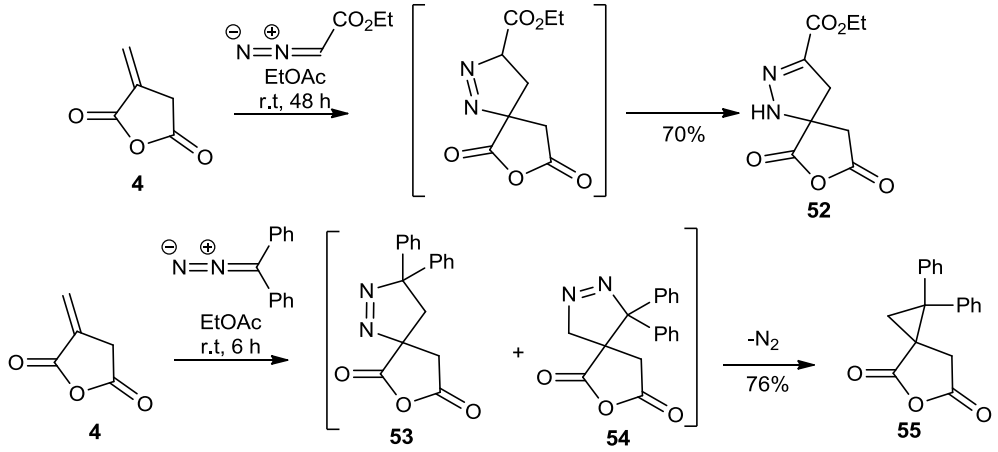
Scheme 14

The 1,3-dipolar cycloaddition of nitrone **50** with itaconic anhydride **4** leads exclusively to the cycloadduct **51**, which can undergo facile methanolysis to give the same product of the reaction between dimethyl itaconate (**18**) and nitrone **50** (Scheme 15).[62] The 1,3-dipolar cycloaddition of ethyl diazoacetate with **4** gives the spiropyrazone **52** and interestingly, when diphenyldiazomethane is used as the dipole, the two resulting spiropyrazones **53** and **54** undergo facile loss of nitrogen, providing the spirocyclopropane **55** (Scheme 16).[63] The 1,3-

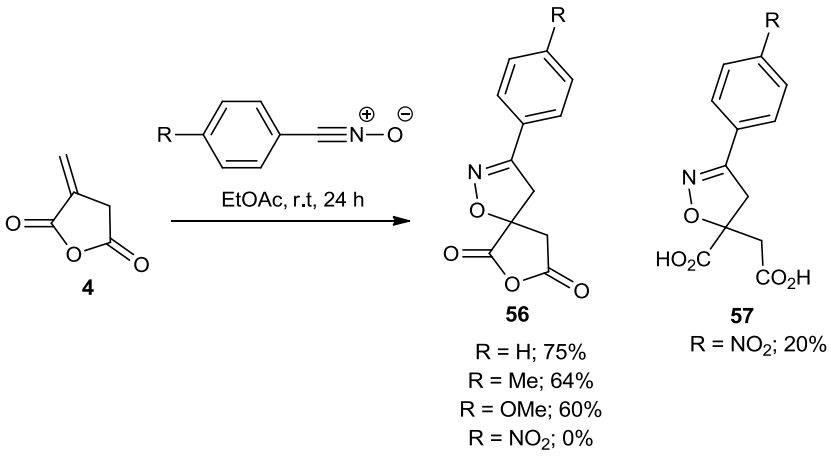
dipolar cycloaddition of phenylnitrile oxide with **4** was first reported in 1952[64] with Ciamal and co-workers later demonstrating that various substituted phenylnitrile oxides work in this process, forming spiroheterocycles **56**. In the *para*-nitro case, the ring opened product **57** was obtained (Scheme 17).[65] The same authors also examined the use of *C*-aroyl-*N*-phenylnitrones **58** in the dipolar cycloaddition with **4**, ultimately providing spiroheterocycle **59** with complete regio- and stereoselectivity in preference to **60** (Scheme 18).[65] During the preparation of novel pyrrolizidinone-based dipeptide isosteres, the 1,3-dipolar cycloaddition of nitrone **61** with dimethyl itaconate was examined. The isoxazoline product **62** arising from this cycloaddition was isolated as a single diastereomer. N–O bond cleavage of **62** with concomitant cyclization gave a mixture of pyrrolizidinone **63** and indolizidinone **64**, with a good yield and ratio favouring the desired 5-*exo*-*trig* pathway (**63**) observed when the hydrogenolysis-cyclization was conducted in the absence of acetic acid (Scheme 19).[66]



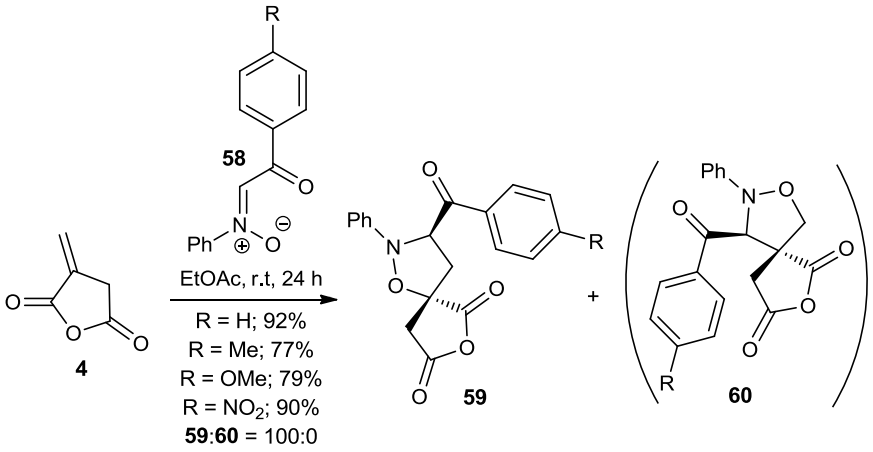
Scheme 15



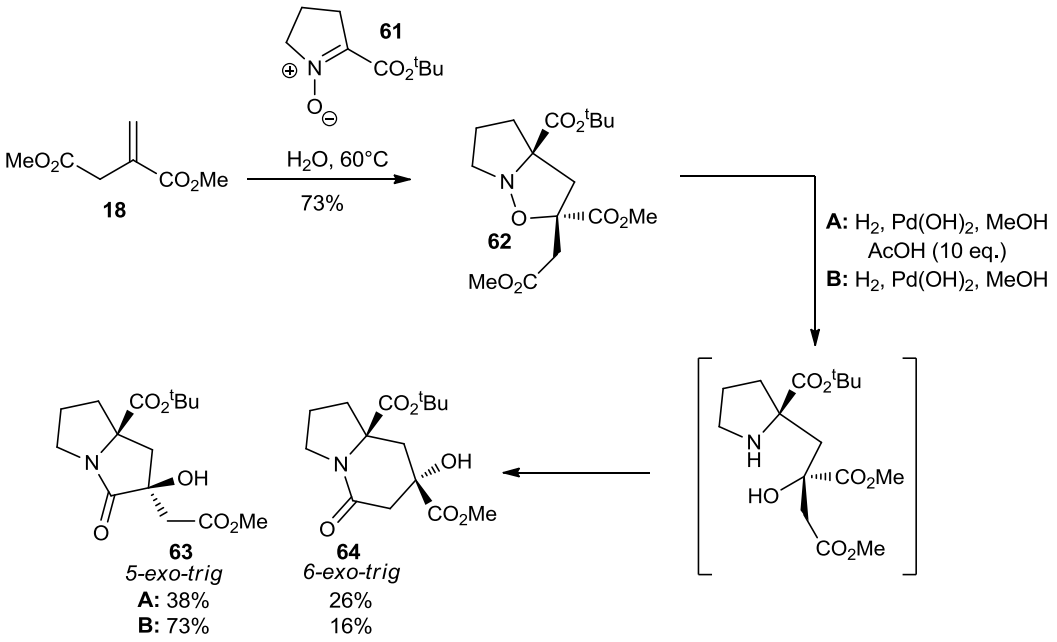
Scheme 16



Scheme 17



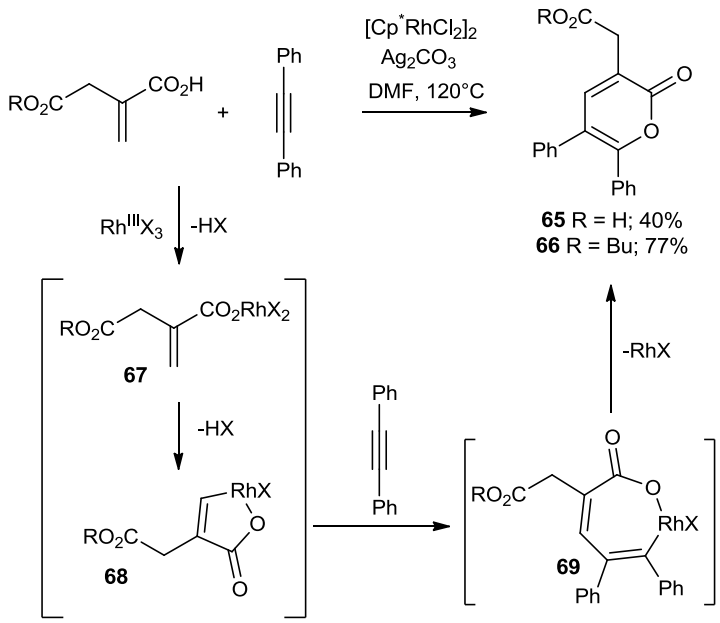
Scheme 18



Scheme 19

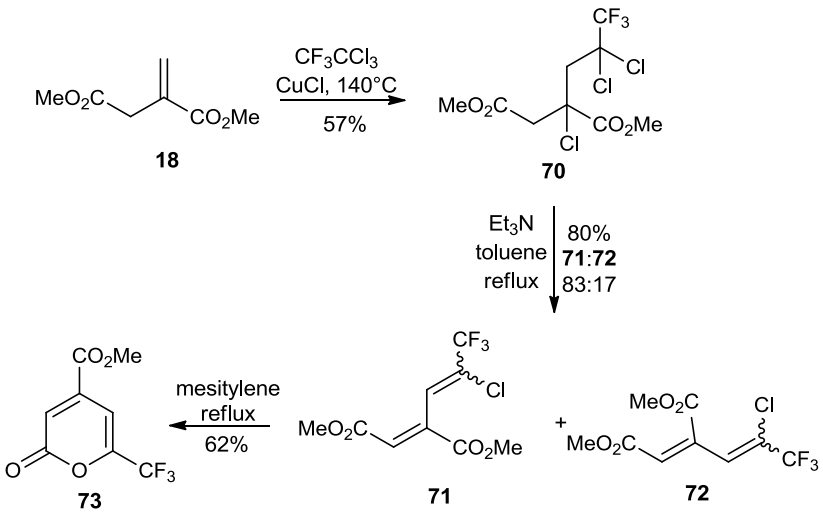
3. Six-Membered Heterocycles

The rhodium-catalysed oxidative coupling between diphenylacetylene and two separate itaconic acid derivatives affords the α-pyrones **65** and **66** (Scheme 20).[67] The mechanism for this interesting transformation commences with formation of rhodium carboxylate **67** followed by cyclorhodation to give rhodacycle **68**. Alkyne insertion gives the 7-membered rhodacycle **69** which upon reductive elimination affords the α-pyrone products.



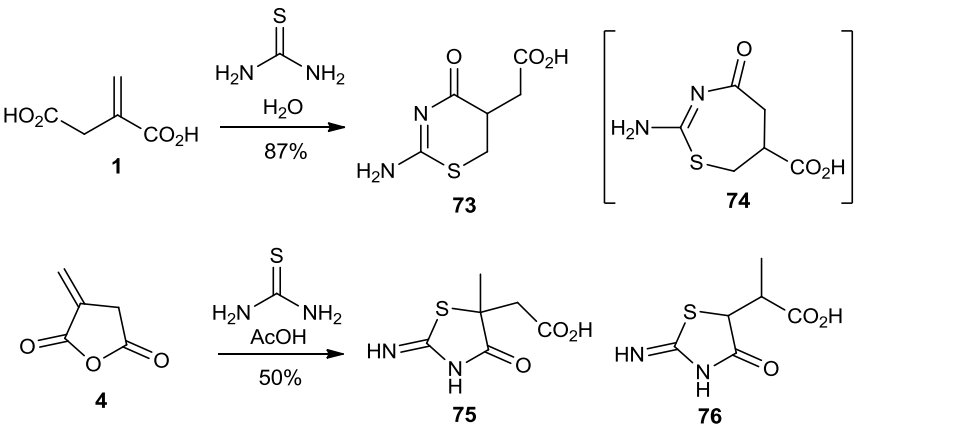
Scheme 20

The copper chloride-catalysed addition of 1,1,1-trichloro-2,2,2-trifluoroethane to dimethyl itaconate (**18**) affords adduct **70**. Upon treatment of **70** with base, an inconsequential mixture of butadienes **71** and **72** is obtained, which upon heating cyclize to form the trifluoromethylated pyrone **73** (Scheme 21).[68] The pyrone **73** serves a versatile diene in the Diels-Alder reaction, facilitating access to an array of [4+2]-cycloadducts bearing a trifluoromethyl group. In general, 2-pyrones are highly sought synthetic intermediates as they participate in cycloaddition reactions with alkynes, generating valuable benzene derivatives.[69]



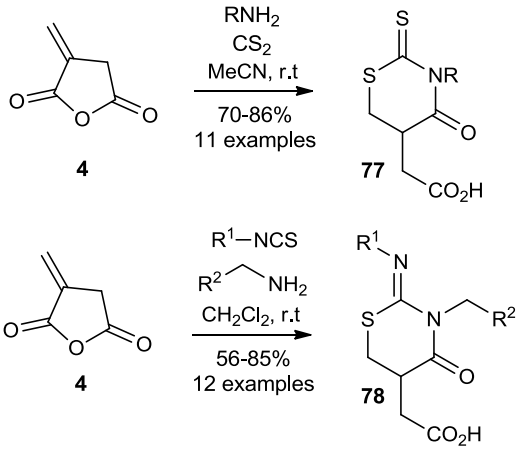
Scheme 21

As alluded to previously in this review, itaconic acid and itaconic anhydride often produce distinct products when subjected to the same reaction conditions, with Scheme 22 showing an excellent example of this phenomenon. The reaction of itaconic acid (**1**) with thiourea has been found to give the 2-amino-1,3-thiazin-4-one **73**,[70] rather than the 2-amino-1,3-thiazepine-4-one **74** acid originally proposed some 20 years earlier[71] (Scheme 22). The imino-tautomer of **73** is readily available by changing the reaction solvent from water to acetic acid. Interestingly, when itaconic anhydride reacts with thiourea in acetic acid at reflux, as a mixture of 2-iminothiazolidine-4-ones **75** and **76** are obtained (Scheme 22).[70] One can envisage that upon hydrolysis of 2-iminothiazolidine-4-ones **75** and **76**, thiazolidinediones would be obtained, the key heterocycle in a series of drugs known as glitazones used to treat type 2 diabetes mellitus.[72]



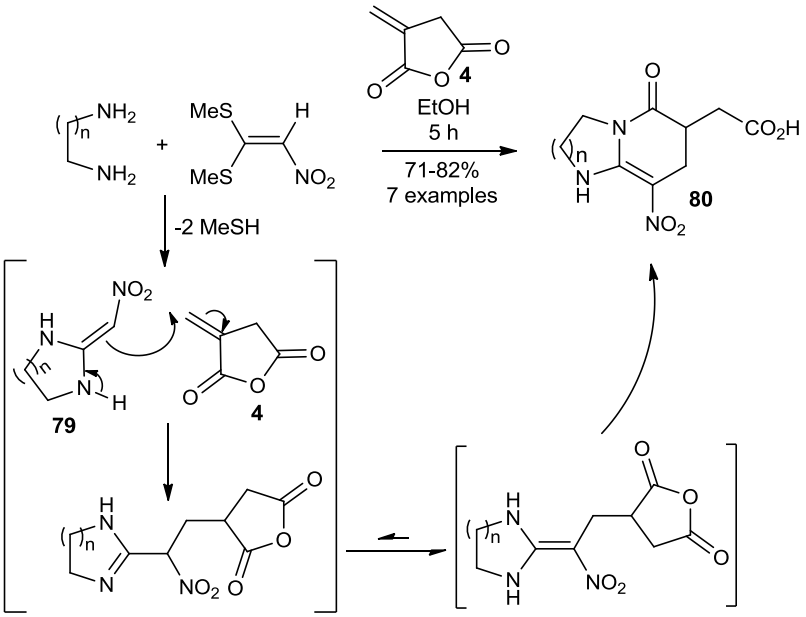
Scheme 22

4-Oxo-2-thioxo-1,3-thiazinanes (**77**) are accessible from the reaction between itaconic anhydride, carbon disulfide and primary amines.[73] Replacing carbon disulfide in the aforementioned process with isothiocyanates provides access to (4-oxo-1,3-thiazinan-5-yl)acetic acids (**78**)[74] (Scheme 23).



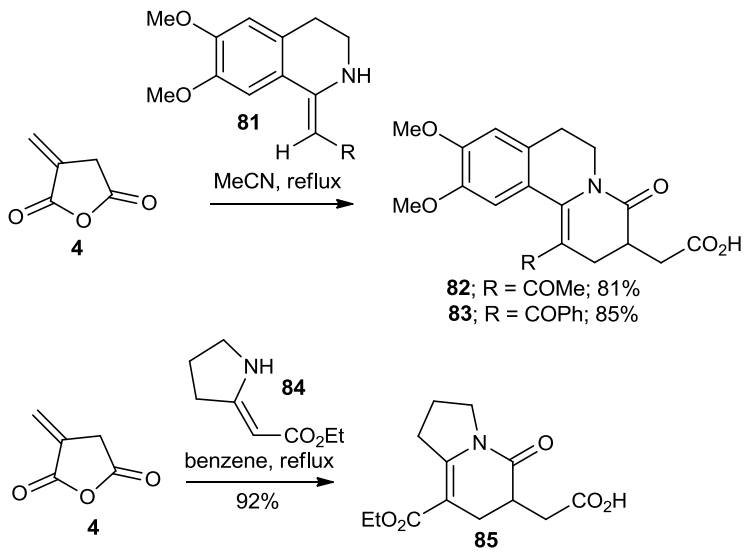
Scheme 23

The reaction of diamines with nitroketene thioacetal produces nitroketene aminals **79** which upon exposure to itaconic anhydride, affords pyrido[1,2-*a*]-fused 1,2-diazaheterocycles **80**. The authors propose the reaction proceeds via an aza-ene-tautomerization-ring closure sequence (Scheme 24).[75]



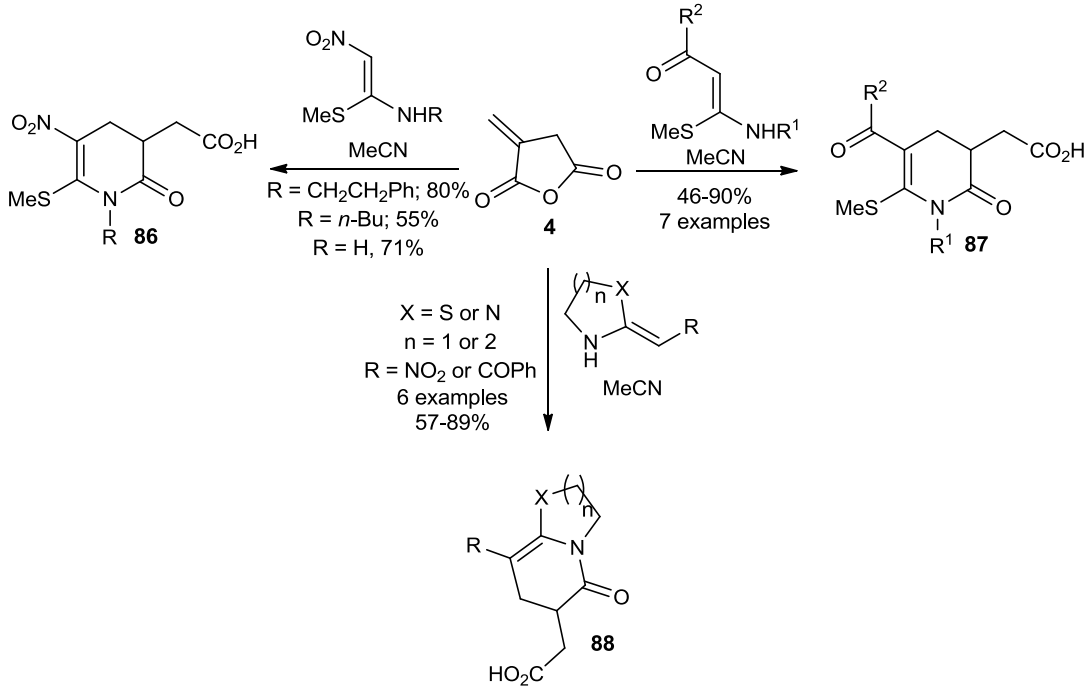
Scheme 24

The aza-annulation of enaminones **81** with itaconic anhydride provides substituted benzo[*a*]quinolizinones **82** and **83** (Scheme 25).[76] In a related process, ethyl pyrrolidin-2-ylideneacetate **84** is converted to the tetrahydroindolizinone **85** upon treatment with itaconic anhydride.[77] Due to the molecular complexity that can be built up in a single step using this reaction, it has inevitably found use in the production of architecturally diverse heterocyclic libraries.[78]

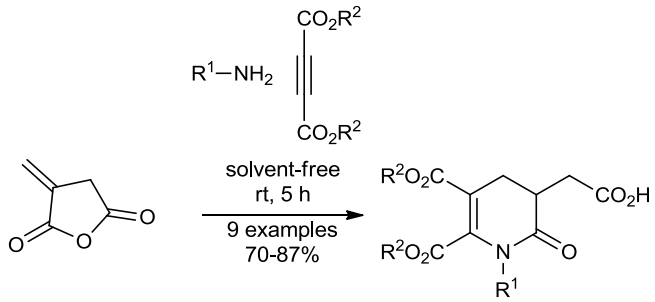


Scheme 25

A detailed study regarding the synthesis of several 2-oxo-(1,2,3,4-tetrahydropyridin-3-yl)acetic acids **86**, **87** and **88** by the reaction of itaconic anhydride with acyclic and cyclic α-oxo- and α-nitro-*N*,*S*- and –*N*,*N*-ketene acetals has been reported (Scheme 26).[79] Compounds bearing this heterocyclic motif are available from the domino reaction between itaconic anhydride, primary amines and acetylenedicarboxylates (Scheme 27).[80]

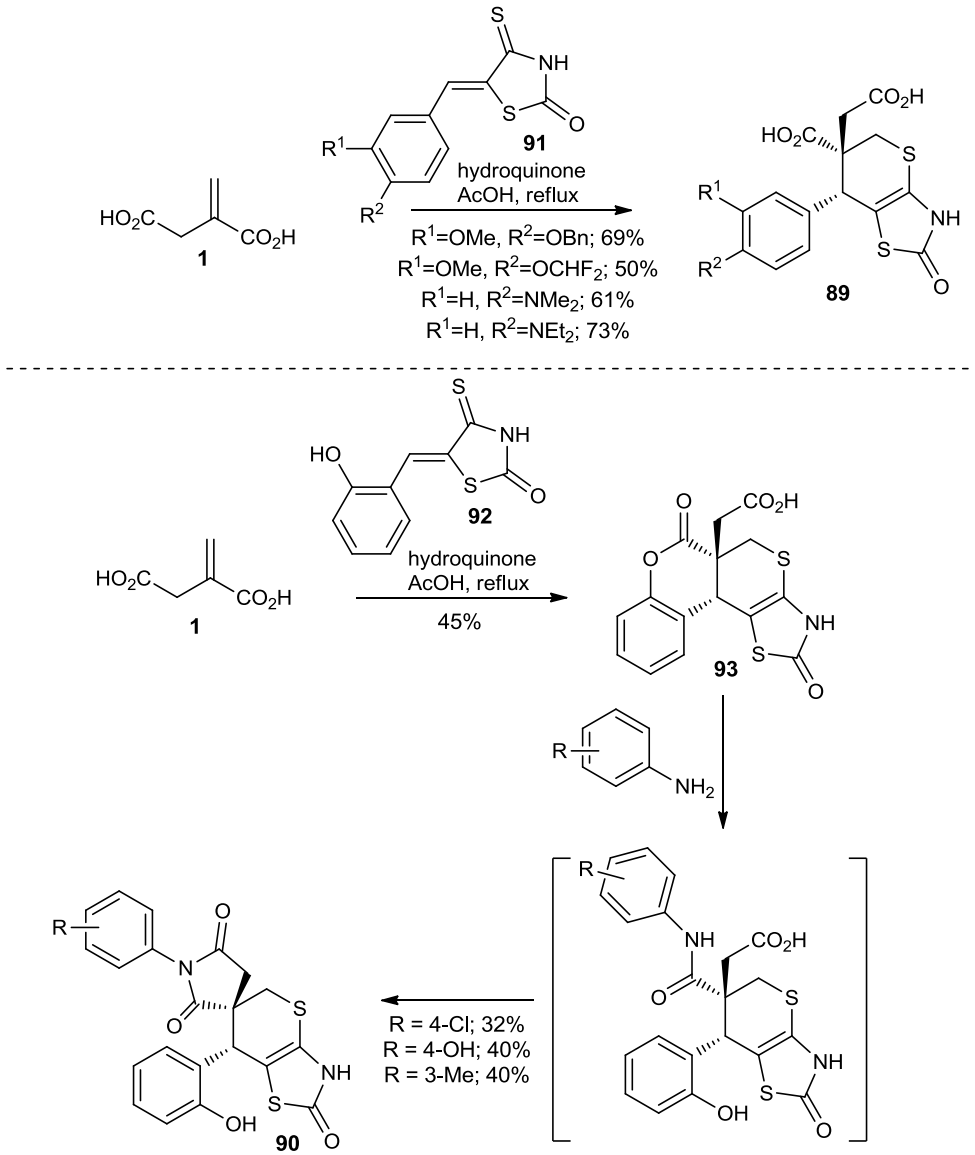


Scheme 26



Scheme 27

In a study that demonstrates the utility of itaconic acid in the rapid construction of complex heterocyclic motifs, several thiopyrano[2,3-*d*]thiazoles **89** and **90** have been synthesized as potential antitrypanosomal agents (Scheme 28).[81] The hetero-Diels-Alder reaction between the 5-arylidene-4-thioxo-2-thiazolidinones **91** and itaconic acid gave the thiopyrano[2,3-*d*]thiazole-6-carboxylic acids **89**. When 5-(2-hydroxyphenylmethylidene)isorhodanine **92** is employed as the diene in this cycloaddition process, cycloadduct **93** is formed which undergoes further reaction with various anilines to give products **90**.

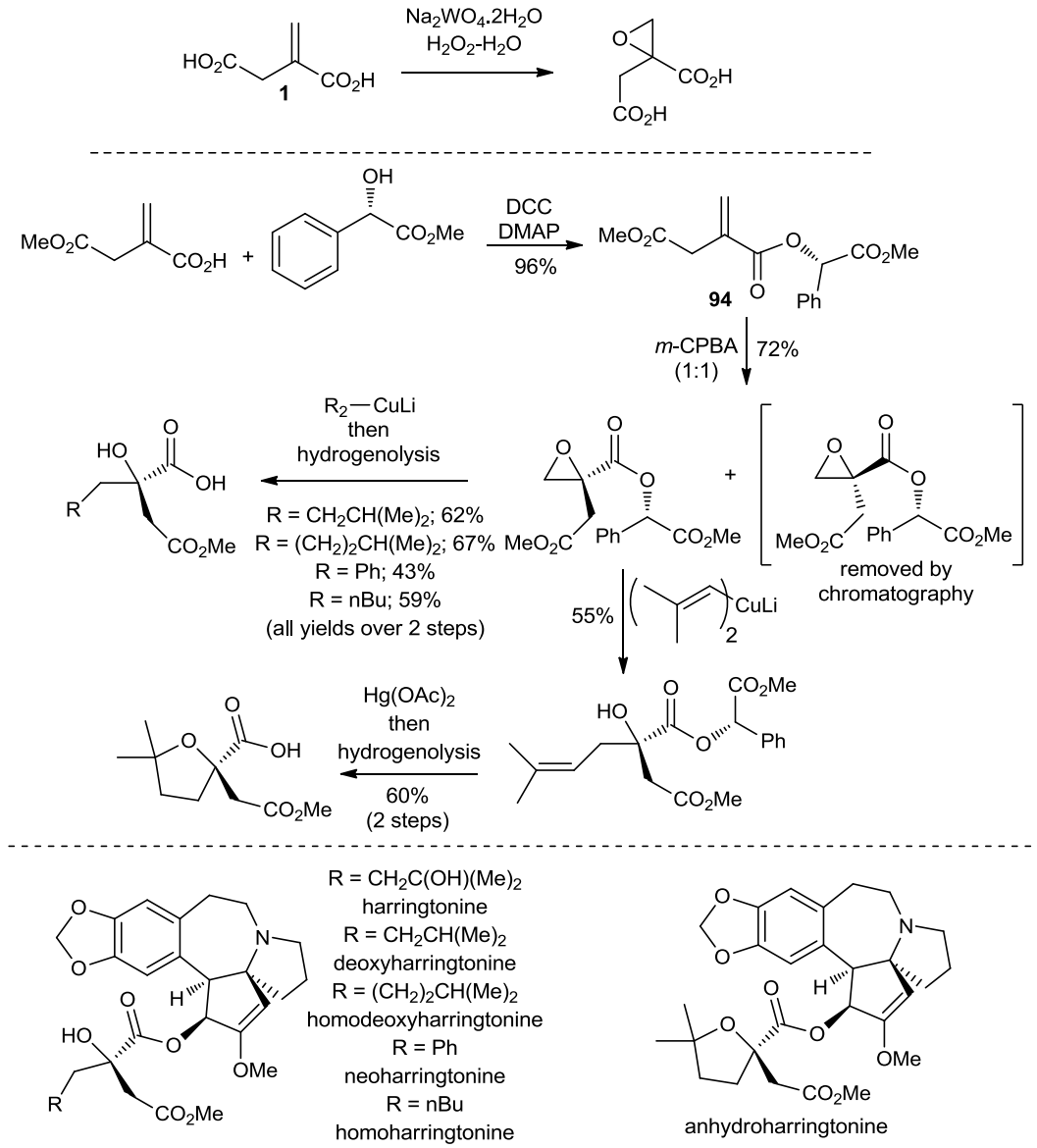


Scheme 28

4. Small and Large Rings

Itaconic acid has also found, albeit rather limited, application in the synthesis of heterocycles other than the 5- or 6-membered examples detailed in sections 1-3. For example, the double bond can be used as a handle with which to conduct epoxidations under tungsten catalysis (Scheme 29).[82] Chiral epoxides can also be accessed, as seen during the synthesis of the optically active side-chains of the *Cephalotaxus* alkaloids deoxyharringtonine, homodeoxyharringtonine, neoharringtonine and anhydroharringtonine (Scheme 29).[83] Esterification of methyl itaconate with (*S*)-methyl mandelate gave diester **94**. The chiral

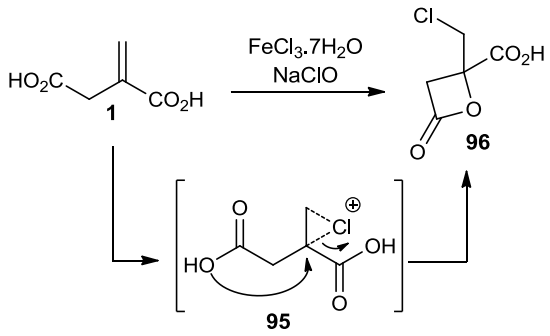
centre was too distant to affect any diastereoselectivity in the resulting epoxidation, but the resulting diastereomers were readily separable by flash chromatography. Ring-opening with different organocuprates provided access to the side-chains of the aforementioned alkaloids.



Scheme 29

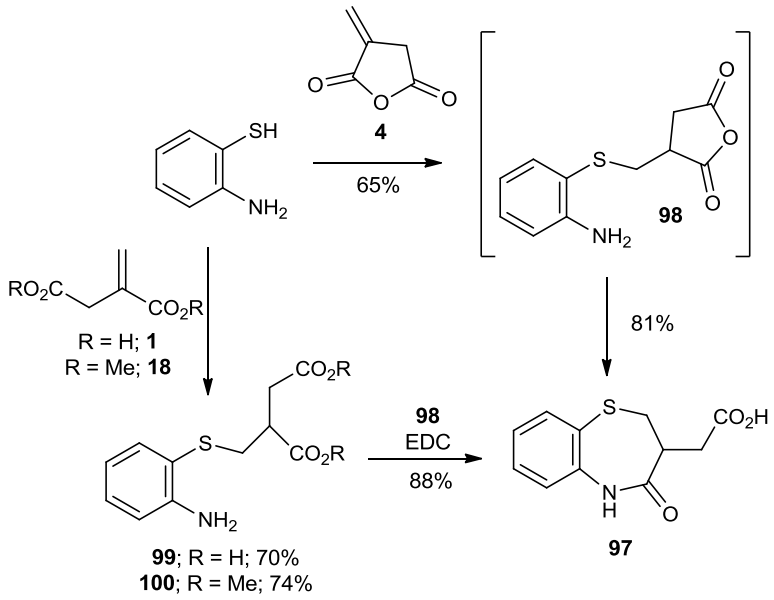
The electrophilic chlorine source generated from sodium hypochlorite and ferric chloride reacts with itaconic acid to form the chloronium ion **95** which upon intramolecular cyclization gives 4-carboxy-4-chloromethyl oxetanone **96** (Scheme 30).[84] 2-Oxetanone, also

known as β-propiolactone is a disinfectant and has been used to sterilize blood plasma, vaccines, tissue grafts, surgical instruments, and enzymes.[85]

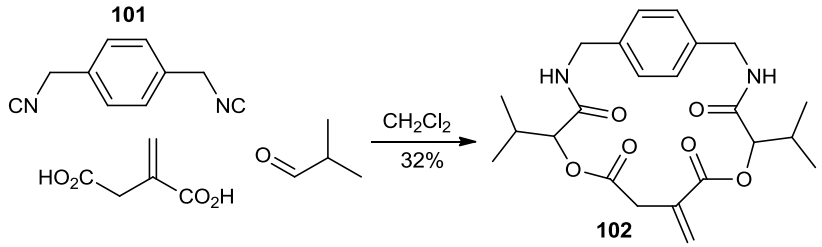


Scheme 30

Benzothiazepinyl acetic acid (**97**) can be accessed in one-pot by heating itaconic anhydride with *o*-aminothiophenol (*o*-ATP), with none of the presumed intermediate **98** observed. Interestingly, itaconic acid and dimethyl itaconate react with *o*-ATP to form the isolable intermediates **99** and **100**, respectively. The diacid **99** undergoes lactamization to **97** in the presence of the coupling agent EDC (Scheme 31).[86] An interesting application of the Passerini three component coupling involves the reaction between itaconic acid, diisocyanide **101** and isobutyraldehyde to give macrocycle **102** (Scheme 32).[87]



Scheme 31



Scheme 32

5. Conclusions

Employing renewable feedstocks in the production of society-reliant chemicals will ensure that current production levels can be sustained well into the future. Herein, we have showcased the remarkable degree of chemical diversity that can be generated from just a single renewable building block, with most examples being single-step or one-pot operations and many employing environmentally favourable reaction conditions. It is hoped this critical review has provided a thought-provoking perspective on the use of biomass-derived building blocks in chemical synthesis.

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