SYNTHESIS OF PYRAZOLO[1,5-*a*]QUINOLINES AND RELATED REDUCED DERIVATIVES

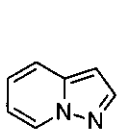
David Barrett

Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co. Ltd.,
2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan
[E.mail: david_barrett@rnd.fujisawa.co.jp]

Abstract - The synthetic approaches employed for the preparation of pyrazolo[1,5-*a*]quinolines and related hydrogenated derivatives are reviewed.

INTRODUCTION

Many synthetic approaches to compounds based on the pyrazolo[1,5-*a*]pyridine skeleton (**1**) have been described, in part due to the broad range of interesting biological activity associated with this heterocyclic system.[1] Particularly prominent examples of pharmaceutically significant compounds include the well known leukotriene D_4 antagonist Ibudilast (**2**)[2] and the adenosine antagonist FK453 (**3**).[3] Amongst possible benzoannelated analogs, pyrazolo[1,5-*a*]quinolines (**4**) are expected to be most similar to **1**, and as such hold the promise of novel biological profiles. However, despite this potential, only scant attention has been paid to this class of heterocycle, the likely result of the relatively few well-explored synthetic methods available. The objective of this review is to survey the synthetic methods that have been used to prepare this type of compound, with a particular emphasis on the strategic bonds constructed in the key step and thereby to highlight the rich and essentially untapped potential of this class of compound for development of useful properties. Where information is available, a brief description of the biological properties of the prepared pyrazolo[1,5-*a*]quinoline derivatives is also included, although readers are directed to the original literature for more complete information.



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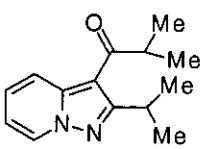
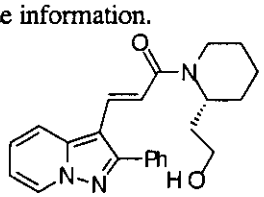
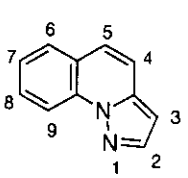


Ibudilast (2)



FK 453 (3)

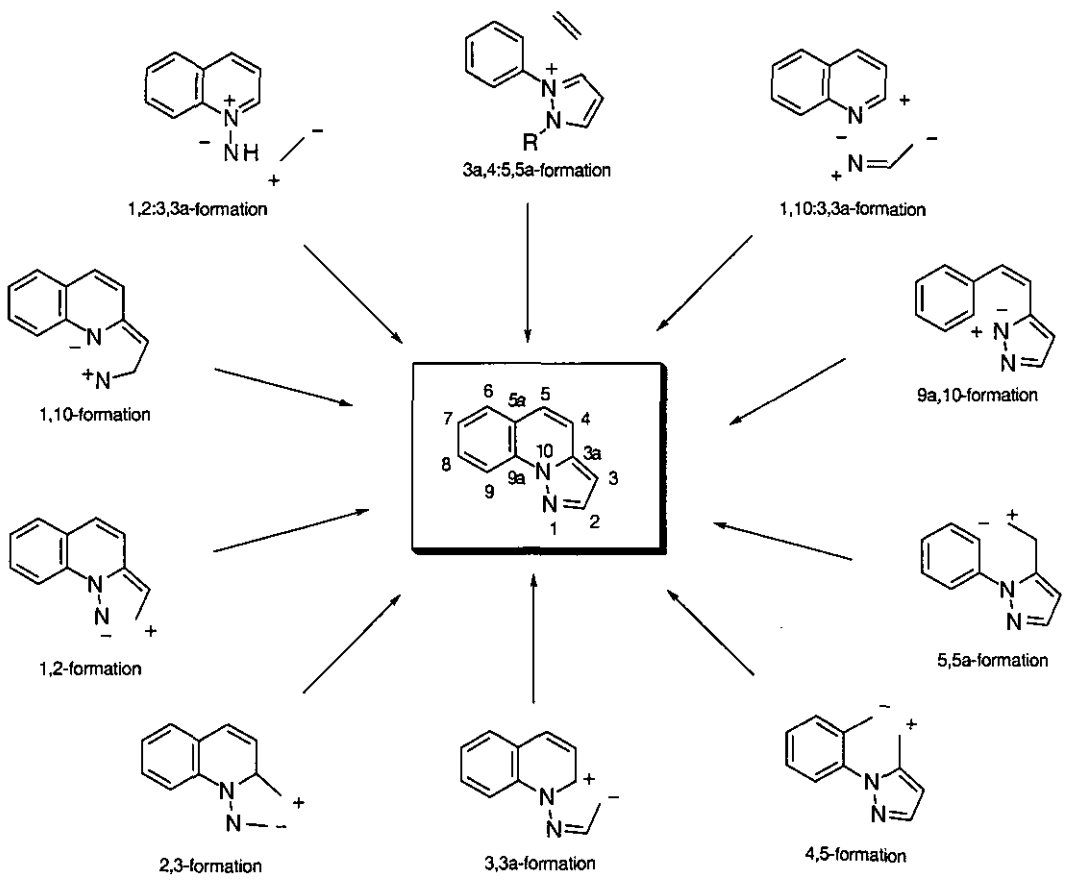


4

SYNTHESIS

Reported routes to the pyrazolo[1,5-*a*]quinoline skeleton, including various related reduced analogs can be conveniently classified as shown in Scheme 1. The most widely investigated route involves the two-bond construction of the 1,2 and 3,3a bonds *via* 1,3-dipolar cycloaddition reaction between a 1-iminoquinolinium salt, conveniently generated from a quinoline precursor, and a suitable dipolarophile acceptor species. Other routes predominantly involve the construction of a single bond to generate the tricyclic ring system, with formation of the 3,3a and 5,5a bonds being particularly well represented. For the purposes of this review, syntheses are classified according to which bond(s) of the pyrazolo[1,5-*a*]quinoline ring system are formed in the process that produces the tricyclic array. In certain cases, a complex series of steps tends to obscure this simple classification, nevertheless mechanistic speculation leads to a fairly rational categorization.

Scheme 1 Disconnections for Construction of Pyrazolo[1,5-*a*]quinolines

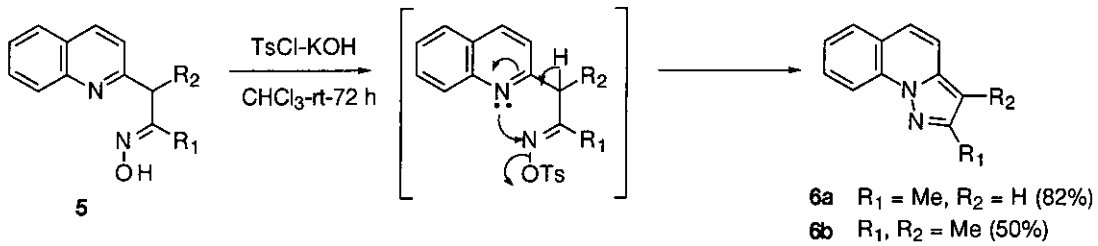


One-Bond Construction

1,10-Bond Formation

A Beckmann rearrangement of the *anti*-oximes (**5**) using TsCl-KOH gave the pyrazolo[1,5-*a*]quinolines (**6a**) and (**6b**) in 82 and 50% yields respectively (Scheme 2).[4] Several related *syn*-oxime isomers gave only the normal Beckmann-rearranged acetanilides, with no N-N bond formation, when treated with PPA. These results indicate that a concerted process is likely in the N-N bond formation *via* displacement of the tosylate group.

Scheme 2



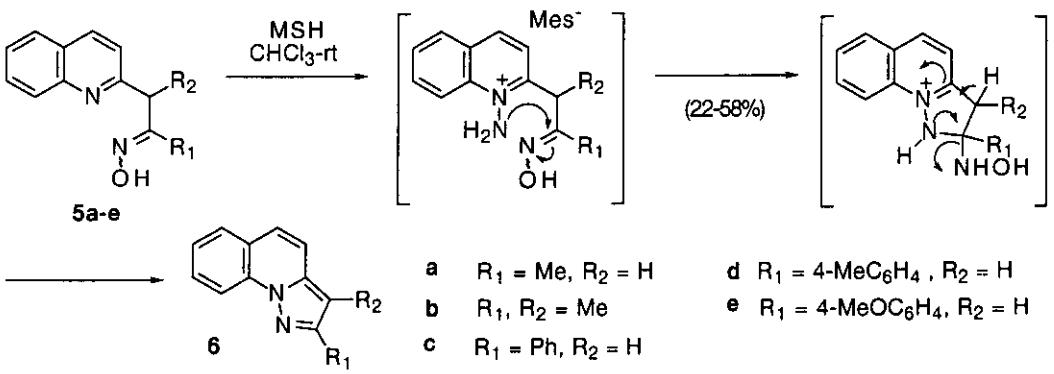
5

6a R_1 = Me, R_2 = H (82%)
6b R_1, R_2 = Me (50%)

1,2-Bond Formation

In contrast to the Beckmann reactions with TsCl, a *syn,anti* mixture of oximes (**5a-e**) reacted with *O*-mesitylenesulfonylhydroxylamine (MSH), independent of oxime configuration, to afford the pyrazolo[1,5-*a*]quinolines (**6a-e**) in 22-58% yields (Scheme 3).[4,5] This reaction was presumed to occur *via N*-amination of the quinoline nitrogen and subsequent cyclization to the oxime double bond, followed by expulsion of hydroxylamine, since hydroxylamine mesitylene sulfate could be isolated from the corresponding reaction leading to a pyrazolo[1,5-*a*]pyridine.[5]

Scheme 3



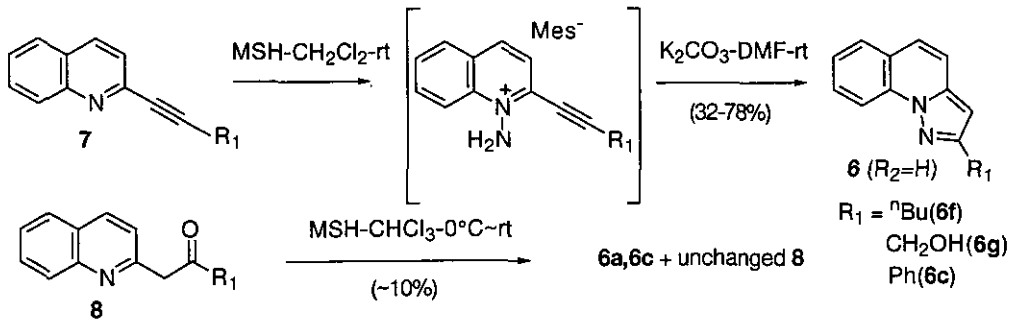
5a-e

6

a R_1 = Me, R_2 = H
b R_1, R_2 = Me
c R_1 = Ph, R_2 = H
d R_1 = 4-MeC_6H_4 , R_2 = H
e R_1 = 4-$MeOC_6H_4$, R_2 = H

Variations on this theme employing acetylenes (**7**)[6,7] or ketones (**8**)[5] in place of the oxime are known (Scheme 4). In the case of ketones (**8**), only very low yields were obtained; these were attributed to the ready enolization of the keto-moiety *via* intramolecular hydrogen bonding. The 2-step preparation involving acetylenes (**7**) was claimed to be a particularly reliable procedure with potential broad applicability.[6,7]

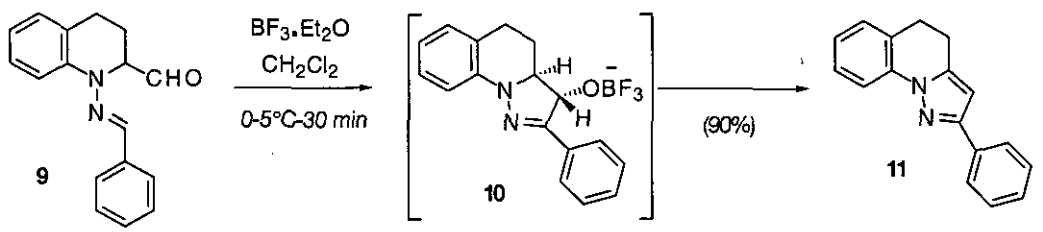
Scheme 4



2,3-Bond Formation

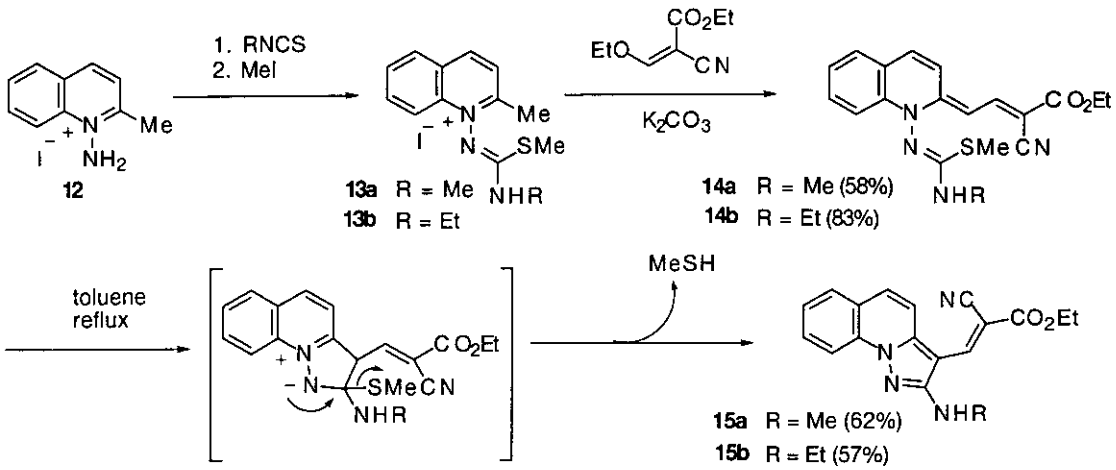
Pyrazole ring formation by Lewis acid-mediated intramolecular reductive coupling of a hydrazonyl group to a formyl group has been applied to the synthesis of 4,5-dihydropyrazolo[1,5-*a*]quinoline (**11**) (Scheme 5).[8,9] Whilst detailed investigation of the reaction pathway was only reported for the case leading to pyrazolo[1,5-*a*]indole derivatives, it seems likely that complex (**10**) is an intermediate and undergoes syn-elimination to give dihydro derivative (**11**).

Scheme 5



1-Aminoquinolinium salt (**12**) was readily converted to salts (**13**) as *cis,trans* mixtures in two steps by reaction with an isothiocyanate and methyl iodide. Condensation with ethyl ethoxymethylenecyanoacetate in the presence of base at room temperature afforded the 2-allylidene-1,2-dihydroquinoline derivatives (**14**) in good yield, along with a trace of pyrazolo[1,5-*a*]quinolines (**15**). Thermolysis of **14** in toluene leads to evolution of methanethiol and formation of **15** in good yield (Scheme 6).[10] Mechanistically, a disrotatory electrocyclic cyclization, followed by elimination of methanethiol explains formation of these products.

Scheme 6



12

13a R = Me
13b R = Et

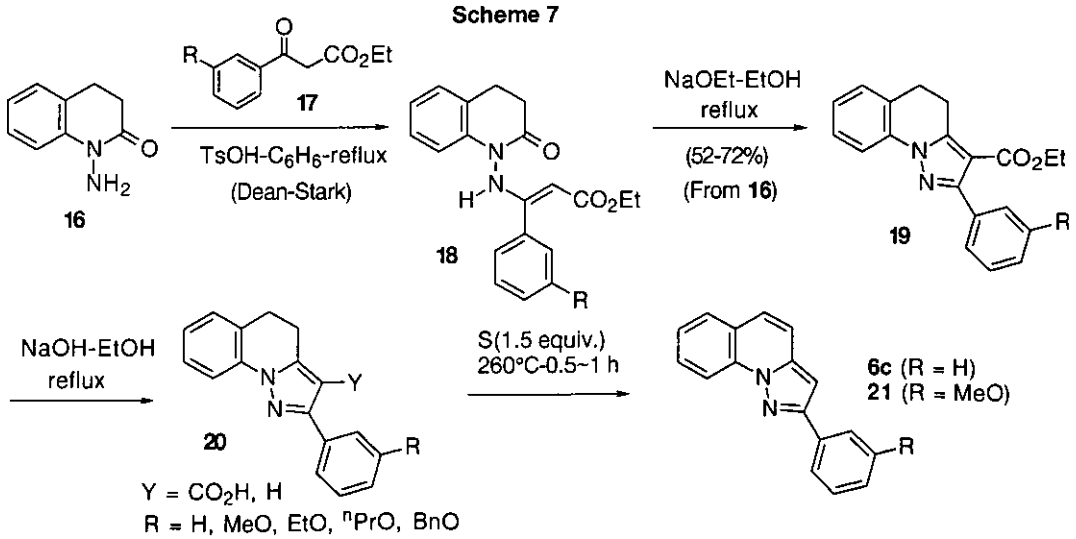
14a R = Me (58%)
14b R = Et (83%)

15a R = Me (62%)
15b R = Et (57%)

3,3a-Bond Formation

An approach based on closure of the 3,3a bond as the key step is known. As part of a program to discover potent antifertility agents, a series of 2-arylpyrazolo[1,5-*a*]quinolines (**20**) and (**21**) have been described.[11] Enamine derivatives (**18**), readily prepared from 1-amino-3,4-dihydroquinolin-2(1*H*)-one (**16**) and aryl β-keto esters (**17**), cyclized smoothly under basic conditions to give 4,5-dihydro derivatives (**19**) in 52-72% yields (Scheme 7). Further transformations, including ester hydrolysis, thermolytic decarboxylation, and dehydrogenation then provided pyrazolo[1,5-*a*]quinoline derivatives (**20**), (**21**), and (**6c**). The most potent biological effect was displayed by methoxy derivative (**21**); showing an ED_{50} of 0.9 mg/kg/day/s.c. in a hamster antifertility model.

Scheme 7



16

18

19

20

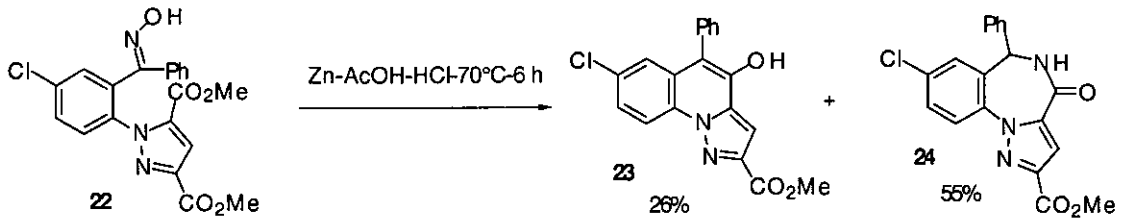
Y = CO_2H, H
R = H, MeO, EtO, ^nPrO, BnO

6c (R = H)
21 (R = MeO)

4,5-Bond Formation

Formation of the 4,5 bond was realized in the reduction of oxime (**22**) with zinc in acetic acid, which afforded the pyrazolo[1,5-*a*]quinoline (**23**) in 26% yield in addition to the expected major product, the pyrazolo[1,5-*a*][1,4]benzodiazepine (**24**) (Scheme 8).[12] No mechanism was offered to explain the formation of this product, although formally a carbanionic species produced by reduction is required.

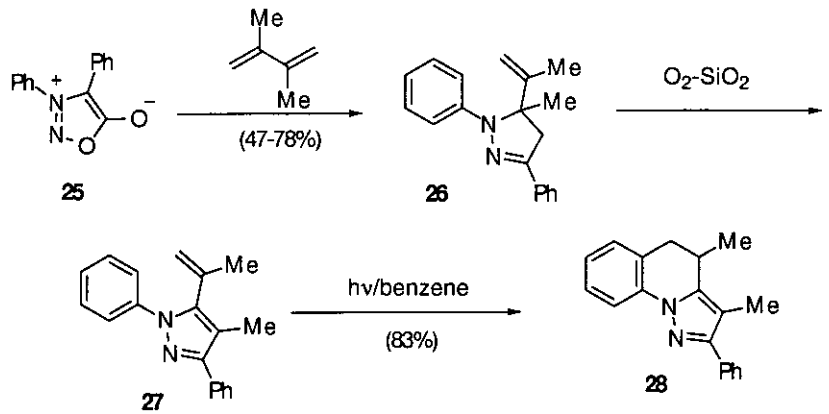
Scheme 8



5,5a-Bond Formation

Photolysis of sydnone (**25**) in the presence of 2,3-dimethyl-1,3-butadiene led by way of the 2-pyrazoline (**26**), to pyrazole (**27**). This compound was cyclized photochemically to generate dihydropyrazolo[1,5-*a*]quinoline (**28**) in 83% yield (Scheme 9).[13] Following on from this observation, Gelin described a general entry to such dihydro derivatives by light-induced ring closure of a variety of 5-(1-alkenyl)-4-ethoxycarbonyl-1-phenylpyrazoles.[14]

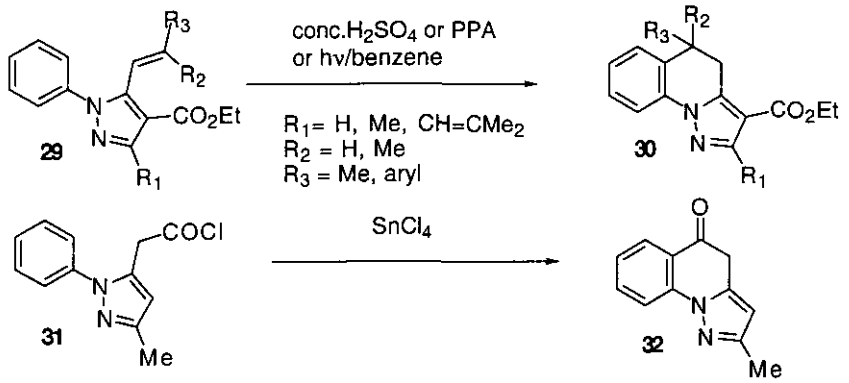
Scheme 9



Gelin also described the acid-catalyzed cyclization of a large number of 5-alkenylpyrazoles (**29**).[15-17] Cyclization with sulfuric acid at room temperature, or with PPA at 80°C, smoothly led to high yields of dihydro derivatives (**30**) (Scheme 10). Since the starting materials for this preparation are readily available

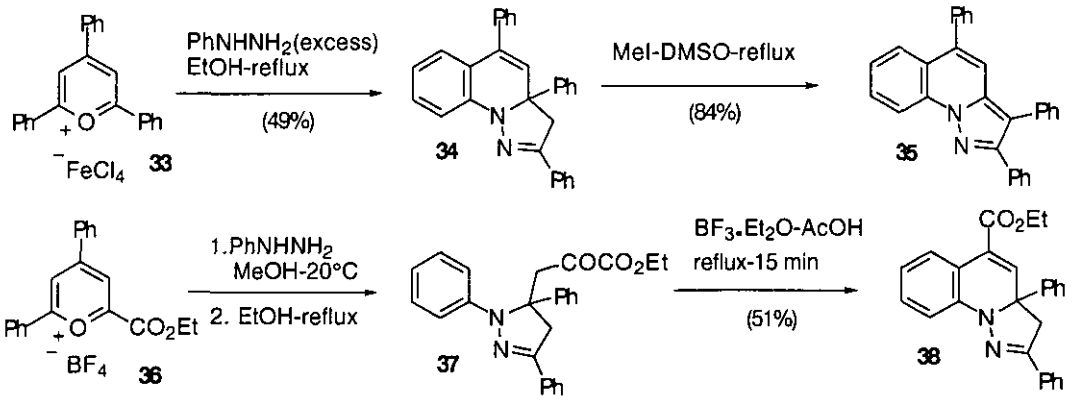
in a short sequence of high-yielding steps, this route is very attractive and of potential wide applicability. Tin tetrachloride-mediated electrophilic cyclization of the acid chloride (**31**) was reported to afford pyrazolo[1,5-*a*]quinoline (**32**) in moderate yield.[18]

Scheme 10



Pyrylium salts have been demonstrated to react with arylhydrazines to afford pyrazolo[1,5-*a*]quinoline skeletons. For example, reaction of 2,4,6-triphenylpyrylium salt (**33**) with an excess of phenylhydrazine in ethanol at reflux afforded **34** in 49% yield. This compound was aromatized by a phenyl migration induced by methyl iodide in refluxing dimethyl sulfoxide, leading to **35** in 84% yield (Scheme 11).[19] In a related investigation, Katritzky demonstrated that ethoxycarbonyl-substituted pyrylium salt (**36**) reacted with phenylhydrazine to give ketone (**37**) *via* a hydrazone intermediate. This material was cyclized in a separate step with boron trifluoride etherate in refluxing acetic acid to afford **38** in moderate yield.[20]

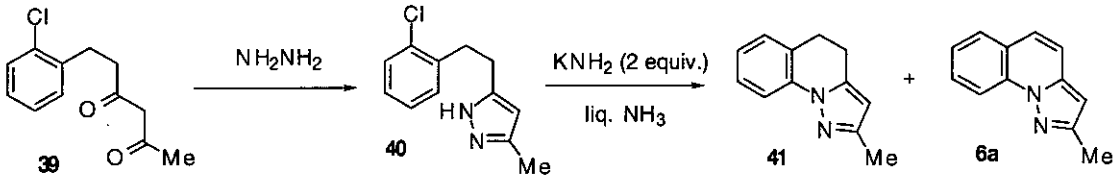
Scheme 11



9a,10-Bond Formation

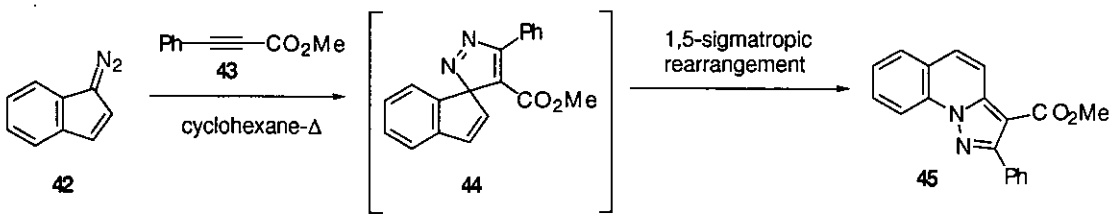
Readily available pyrazole (**40**) reacted with potassium amide to yield the dihydro derivative (**41**) in moderate yield.[18] Oxidized pyrazolo[1,5-*a*]quinoline (**6a**) was produced as a byproduct in varying amounts (Scheme 12). A benzyne intermediate is presumably formed by elimination of hydrogen chloride form the aryl chloride moiety, which is then intercepted by the pyrazole nitrogen.

Scheme 12



1,3-Dipolar cycloaddition reaction of diazoindene (**42**) with acetylenes, e.g. ester (**43**) leads to spiropyrazolines, e.g. **44**, which then undergo spontaneous 1,5-sigmatropic shift of the phenyl group (van Alphen-Huttel rearrangement) with formation of the 9a,10 bond, leading to moderate yields of pyrazolo[1,5-*a*]quinolines, e.g. **45** (Scheme 13).[21-23] Several other products, resulting from a number of competing pathways make this method of more theoretical, rather than preparative interest.

Scheme 13



Two-Bond Construction

1,2:3,3a-Bond Formation

Perhaps the most employed route to the pyrazolo[1,5-*a*]quinoline skeleton is the 1,3-dipolar cycloaddition reaction between a 1-iminoquinolinium species such as **46**, and a suitable dipolarophile, usually an olefin or acetylene (Scheme 14). Examples of dipolarophiles employed, along with products and yields are shown in Table 1. When the same compound has been described by several different researchers, the respective yields and references are shown.

Scheme 14

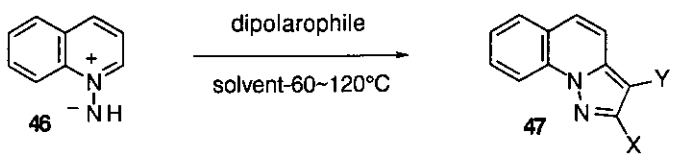
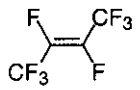
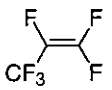
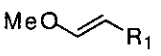
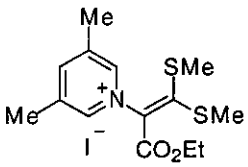
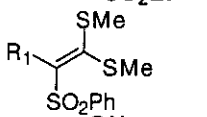
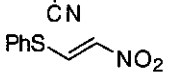


Table 1. Dipolar Cycloadditions of 1-Iminoquinolinium Salt (**46**)

Dipolarophile		Y	Product **47** X	Yield (%)	Reference
	**48**	CF_3	CF_3	31	24
	**49**	CF_3	F	39	24
	**50**	CO_2Me	H	88	25
	51	CN	H	87	
	52	CO-4-BrC_6H_4	H	96	
	53	COPh	H	77	
	**54**	CO_2Et	SMe	87	26
	**55**	CN	SMe	63	27
	56	COMe	SMe	35	
	**57**	CN	CN	83	27
	**58**	H	H	14.3	28
		NO_2	H	58.2	
$\equiv$—CO_2Me	**59**	CO_2Me	H	27	29
				38	30
Ph—$\equiv$—CO_2Et	**60**	CO_2Et	Ph	44	30
MeO_2C—$\equiv$—CO_2Me	**61**	CO_2Me	CO_2Me	10	29
				60	30
				64	31
PhCO—$\equiv$—COPh	**62**	PhCO	PhCO	80	32

Inspection of the results summarized in Table 1 indicates clearly that the regioselectivity of cycloaddition in the case of unsymmetrical dipolarophiles is characteristic, and noteworthy, and can be interpreted as an

initial addition to the most electron-deficient terminus, prior to formation of the 3,3a bond and aromatization. Overall, the best yields seem to result from using the enol ether derivatives (**50-53**); excellent yields of single regioisomers resulted.[25] In this particular paper, Tominaga and co-workers succeeded in converting the 3-methoxycarbonylpyrazolo[1,5-*a*]quinoline cycloadduct into the parent heterocycle by ester hydrolysis (10% NaOH-MeOH-reflux) and decarboxylation (PPA-100°C) in 72% yield. The same compound was obtained in 14.3% yield when 1-nitro-2-phenylthioethylene (**58**) was employed as the dipolarophile,[28] the major product in this case being the 3-nitropyrazolo[1,5-*a*]quinoline (58.2%). Presumably the formation of the free parent heterocycle in this case was the result of a competing elimination of nitrous acid, prior to dehydrogenation. Fluorinated dipolarophiles (**48**) and (**49**) react with elimination of HF in moderate yield. Highly functionalized dipolarophiles, such as **54-57** also give very good yields of cycloadducts.

Despite the fact that the 1-iminoquinolinium 1,3-dipole structure is represented as **46**, Huisgen showed that reaction of the 1-aminoquinolinium salt precursor with a base at low temperature in the absence of a dipolarophile generates dimeric species which, under the high temperature conditions break down to the free dipoles which then participate in the cycloaddition.[30] A particularly interesting method for preparation of the cycloadduct from dimethyl acetylenedicarboxylate (DMAD) was described by Yamashita and co-workers.[31] A 64% yield of cycloadduct was obtained by first reacting the 1-aminoquinolinium iodide salt with 2,5-dimethyl-3,4-diphenylcyclopentadienone to yield an isolable 1,3-dipolar cycloadduct. This material then reacted in a separate step with DMAD to yield the 2,3-dimethoxycarbonylpyrazolo[1,5-*a*]quinoline. Mechanistically, the second step was interpreted as a 1,3 addition-retro 1,3 addition double process with the cyclopentadienone being selectively eliminated from the 1:1 adduct and trapped by DMAD. For reasons that are not entirely clear, the same pyrazolo[1,5-*a*]quinoline derivative was only obtained in 10% by Tamura and co-workers.[29]

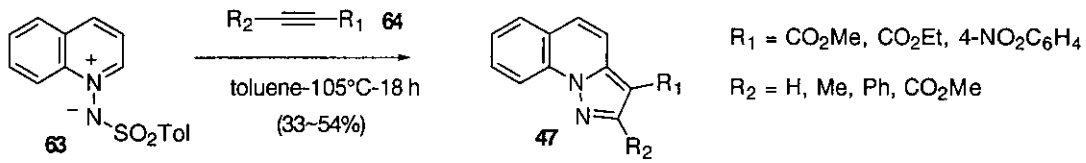
In 1,3-dipolar cycloaddition reactions with normal olefinic and acetylenic dipolarophiles, a dehydrogenation (net oxidation) reaction must take place in to obtain the fully aromatic system. This is possibly promoted by air, however, with an increase in the number of electron deficient substituents, the isolated yields improve dramatically indicating the greater lability of electron deficient dihydro adducts.

For the most part, the pyrazolo[1,5-*a*]quinoline products from these cycloadditions have not been used for investigation of further chemistry, however in a particularly notable exception to this, Potts and co-

workers[32] described a particularly elegant series of transformations of 2,3-dibenzoylpyrazolo[1,5-*a*]quinoline, resulting from reaction of **46** with dibenzoylacetylene.

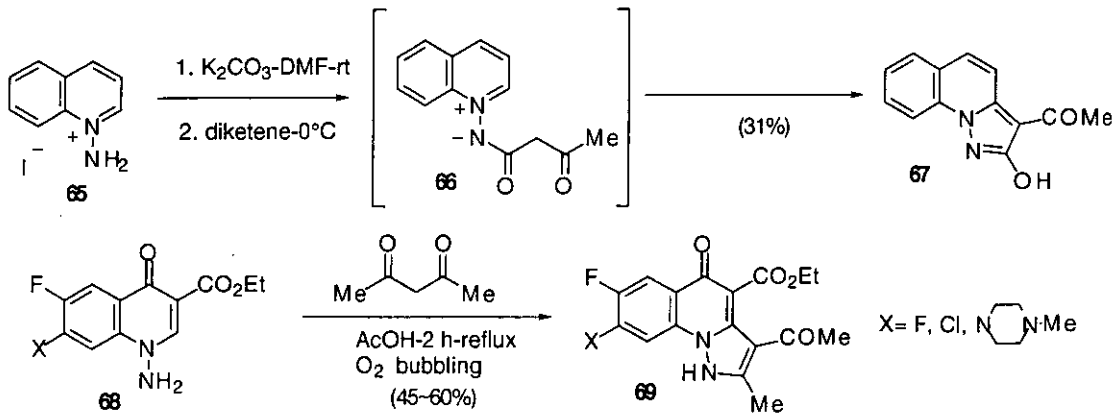
A modification of the standard cycloaddition, employing tosylated quinolinium imine (**63**) as the 1,3-dipole component was described by Sundberg and Ellis, and is depicted in Scheme 15.[33] This salt underwent smooth cycloaddition with acetylenes (**64**) leading to **47** in moderate yield. An elimination step completes the aromatization at the final stage, rather than the usual air mediated dehydrogenation in the reactions with the non-tosylated imine species.

Scheme 15



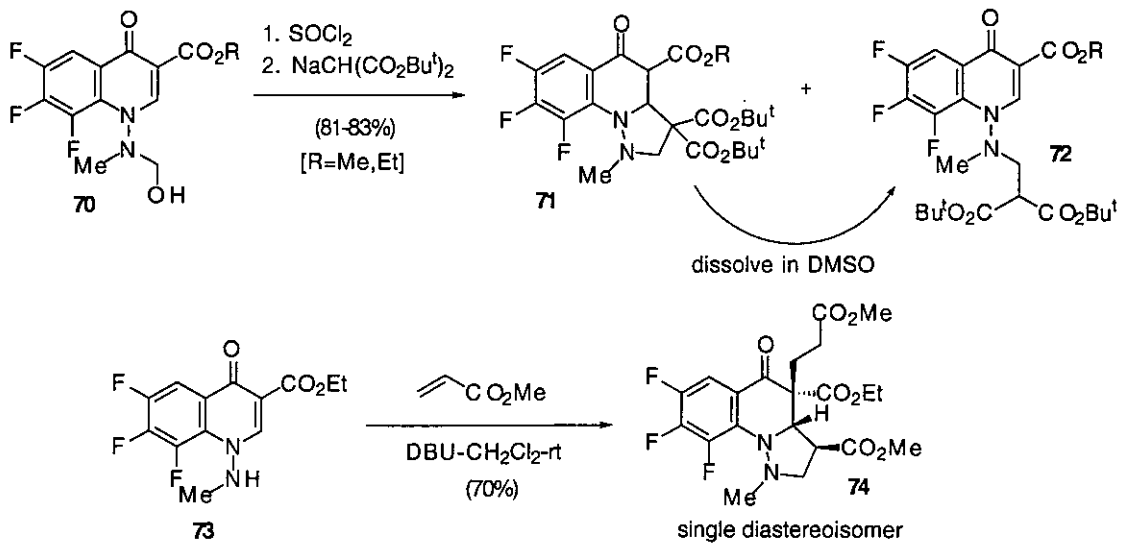
Reaction of 1-aminoquinolinium salt (**65**) with potassium carbonate followed by diketene afforded 2-hydroxy-3-acetylpyrazolo[1,5-*a*]quinoline (**67**) in 31% isolated yield (Scheme 16).[34] Intermediate 1-(*N*-acetoacetylimino)quinolinium salt (**66**) was not isolated. In related work, Russian workers described the one-step synthesis of pyrazolo[1,5-*a*]quinolines (**69**) by reacting 1-aminoquinolones (**68**) with acetylacetone in refluxing acetic acid whilst bubbling oxygen through the reaction mixture. In the absence of bubbling, isolated yields were significantly lower.[35,36] The corresponding reactions with simple cyclic ketones (cyclohexanone, cyclopentanone) led only to hydrazone formation. Reaction with α-dicarbonyl compounds (glyoxal, glyoxylic acid, ethyl pyruvate) resulted in deamination of starting quinolones (**68**).

Scheme 16



We have developed an efficient synthesis of pyrazolo[1,5-*a*]quinolines as antibacterial agents. Our approach resulted from the serendipitous discovery that labile pyrazolo[1,5-*a*]quinolines (**71**) were the primary products in the conversion of hydroxymethyl derivatives (**70**) to malonates (**72**), precursors for the pyrido[3,2,1-*i,j*]cinnoline class of DNA gyrase inhibitors (Scheme 17).[37,38] Detection of the pyrazolo[1,5-*a*]quinoline structure involved obtaining ^{1}H NMR spectra in $CDCl_3$. When spectra of **71** were obtained in DMSO, irreversible ring opening occurred leading to **72** exclusively. As part of efforts to enhance the stability of the pyrazolo[1,5-*a*]quinoline adduct, reaction of methylamino derivative (**73**) with methyl acrylate afforded the double adduct (**74**) in 70% yield *via* a tandem 1,4-conjugate addition-Michael-Michael addition sequence. Since DBU was used as the base in this reaction, the intermediate mono-adduct could not be isolated, presumably due to the rapid second alkylation. Compound (**74**) was produced as a single diasteroisomer, whose structure was confirmed by a single crystal X-Ray analysis.[39]

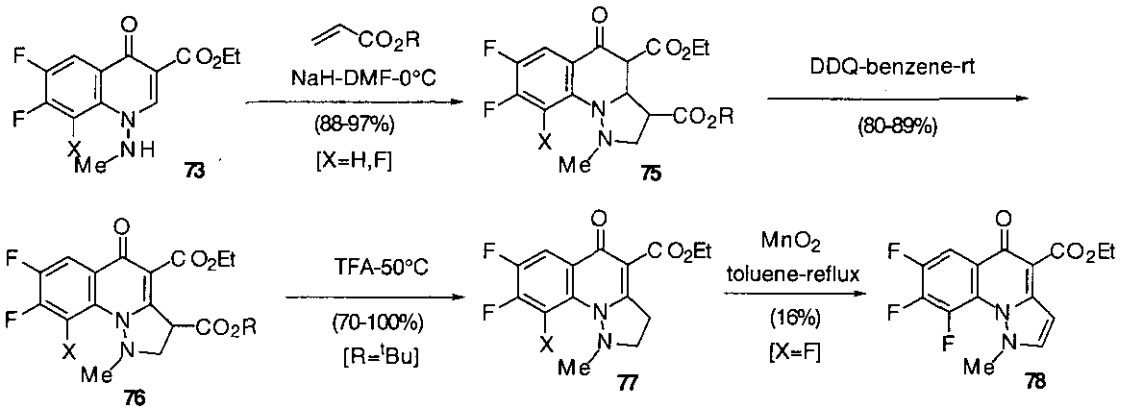
Scheme 17



Condensation reactions with simple acrylate derivatives could be stopped at the tricyclic stage, without further reaction with the Michael acceptor by employing sodium hydride as the base (Scheme 18). In this way, compounds (**75**) were produced as mixtures of diastereoisomers in high yield, whereby the major isomer had an *endo*-orientated ester group indicating a kinetically controlled cyclization. Subsequent transformations yielded tetrahydro derivative (**77**) and dihydro derivative (**78**) by way of quinolone (**76**). Interestingly, **78** displayed long-range coupling in the ^{1}H and ^{13}C NMR spectra between the N1-methyl group and the 8-fluorine substituent, a phenomenon not observed with tetrahydro derivative (**77**). X-Ray

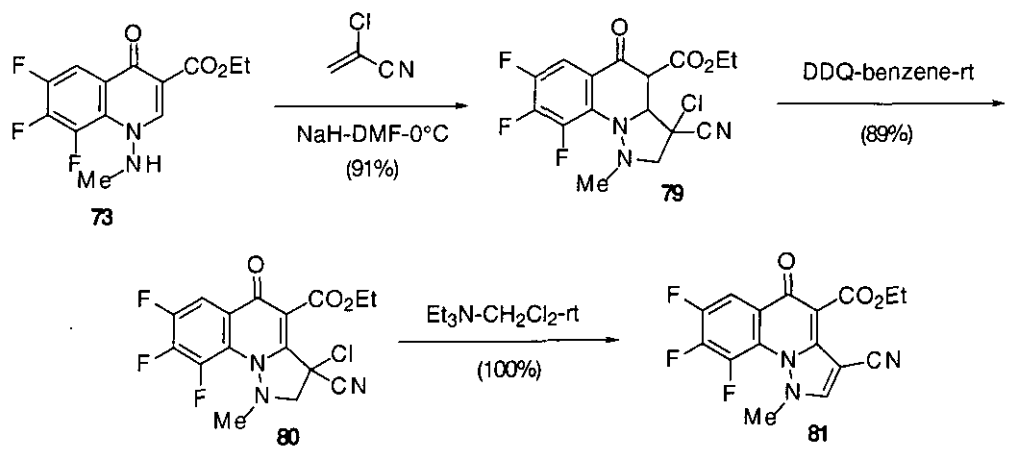
analysis confirmed the structures of both of these novel heterocycles and indicated a close contact between the 8-F and N1-Me groups in **78**.[39,40] Conversion of **77** and **78** to antibacterial agents was achieved by displacement of the 8-F group with secondary amines, such as piperazine and *N*-methylpiperazine and hydrolysis of the 4-ethyl ester group.

Scheme 18



An alternative method of introducing a double bond between C2 and C3 was developed in order to overcome the low chemical conversion that was observed in the oxidation of tetrahydro derivative (**77**). Selection of 2-chloroacrylonitrile as the coupling partner for the tandem 1,4-conjugate addition-Michael addition reaction produced **79** in high yield. DDQ oxidation gave **80** in 89% yield, which then reacted with triethylamine to produce **81** in quantitative yield (Scheme 19). This compound was shown to undergo exclusive *N*-demethylation when heated in acid; methylation (MeI-K_2CO_3) of the resulting product gave exclusively the *O*-methylated pyrazolo[1,5-*a*]quinoline derivative.[39]

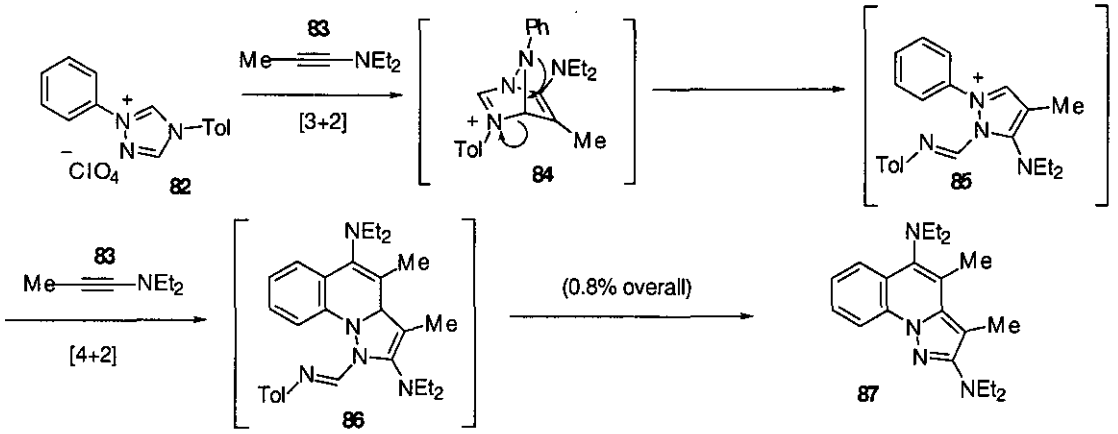
Scheme 19



3a,4:5,5a-Bond Formation

Triazolium salt (**82**) reacts with ynamine (**83**) in a complex series of steps that produce pyrazolo[1,5-a]quinoline (**87**) in low yield (Scheme 20).[41] [3+2] Cycloaddition leading to salt (**84**), followed by ring opening and [4+2] cycloaddition of the resulting pyrazolium salt (**85**) with a second molecule of the ynamine (**83**) yielded **87** after *N*-dealkylative aromatization of **86**.

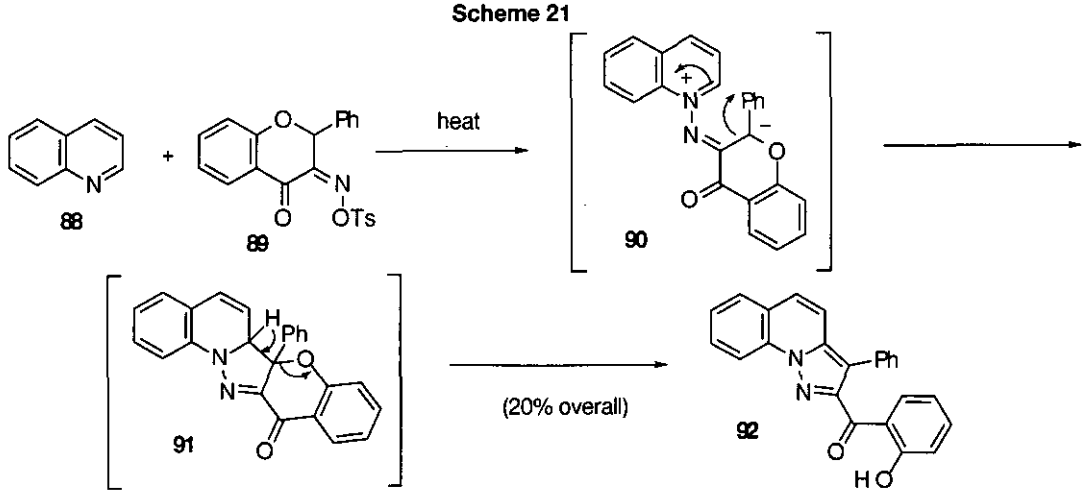
Scheme 20



1,10:3,3a-Bond Formation

An unusual annulation process that results in the net formation of the 1,10 and 3,3a bonds has been disclosed (Scheme 21). Reaction of quinoline (**88**) with the tosylate (**89**) leads to pyrazolo[1,5-*a*]quinoline (**92**) in 20% yield. *N*-Amination leading to **90** is followed by intramolecular cyclization and aromatization *via* ring opening of intermediate (**91**).[42]

Scheme 21



CONCLUSIONS

In this review the synthetic methods reported to date for preparation of pyrazolo[1,5-*a*]quinolines have been surveyed. Whilst the [3+2] cycloaddition approach is the most frequently employed, several new methods have been described that allow for preparation of various reduced analogs, as well as examples bearing substituents. Biological activity for this type of compound remains relatively unexplored, although examples are known.

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