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Full Paper

A New Synthesis of 4,5,6,7-Tetrahydropyrazolo[1,5-*c*] pyrimidines by a Retro-Mannich Cascade Rearrangement

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We discovered a new retro-Mannich reaction of in situ prepared pyrazolopyridines to give pyrazolopyrimidines that have hitherto been underrepresented in the heterocyclic chemistry literature. The isolation of a linear hydrolysis product supports a mechanistic hypothesis for this rearrangement process. In order to establish a broader access and explore potential biological applications for these medicinal chemistry building blocks, we investigated the scope of the reaction and generated small amine- as well as amide-based libraries through reductive aminations and amide couplings, respectively.

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Introduction

In spite of the ubiquitous presence of heterocycles in natural products and their major commercial significance for pharmaceutical and agrochemical products, the universe of heterocyclic compounds has not been exhaustively explored.[1,2] In addition to improved physicochemical properties such as solubility and polarity,[3] metabolic stability[4] and patentability[5] are major driving forces for continued exploration of novel heterocyclic scaffolds.[6] Serendipitous discoveries of cascade reaction pathways often provide access to novel compounds,[7] as exemplified in our own work in the formation of 1,2,4-triazines **1**,[8] isoindolinones **2**,[9] fused bisazoles **3** and **4** and spirocycles **5**,[10,11] pyrrolodiazepines **6**,[12] azatricyclononanes **7**,[13] and other heterocycles[14] (Fig. 1).

During a seemingly routine attempt to prepare the 4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*c*]pyridine **8** from hydrazine and α,γ-diketoester **9**,[15] we obtained instead the 4,5,6,7-tetrahydropyrazolo[1,5-*c*]pyrimidine **11** as the major product (Scheme 1). A subsequent literature search revealed that these heterocycles are relatively rare, and only a few synthetic approaches have been reported, none of which used a readily available precursor such as Claisen product **9**. For example, the structurally most closely related pyrazolopyrimidine **14** was prepared in a [8π + 2π] cycloaddition reaction of diazafulvenium methide **13** with *N*-benzylidenebenzenesulfonamide (Scheme 2).[16]

As a direct consequence of the rarity of synthetic approaches to 4,5,6,7-tetrahydropyrazolo[1,5-*c*]pyrimidines, no information about their biological properties is available. However, it is likely that they can become useful building blocks in medicinal chemistry or exhibit biological activities on their own. For example, the arene-fused tricyclic 5,6-dihydropyrazolo[1,5-*c*] quinazolines **15** were first synthesized in 1962 by Blatter and coworkers[17] and subsequently explored by Cecchi et al.[18] as benzodiazepine receptor ligands and by Poldermann et al.[19] as analgesic agents (Fig. 2).

Inspired by the novelty of the synthetic transformation from **9** to **11** and motivated by the potentially interesting biological profile of compounds containing this underutilized building block, we decided to explore the scope of the transformation and generate a small collection of derivatives.

Experimental

General

All moisture-sensitive reactions were performed under an atmosphere of dry nitrogen and all glassware was either dried in an oven at 140°C or flame-dried under high vacuum before use. 1-Benzyl-3-methylpiperidin-4-one,[20] 9-benzyl-9-azabicyclo [3.3.1]nonan-3-one,[21] 1-benzylazepan-4-one,[22] and 1-benzyl-2,3-dihydroquinolin-4(1*H*)-one[23] were prepared according to literature procedures. THF and Et_2O were dried by distillation over Na/benzophenone, and CH_2Cl_2 and toluene were purified using an alumina filtration system. Reactions were monitored by either ^{1}H NMR at 300 MHz in [D6]DMSO, high-resolution liquid chromatography–mass spectroscopy (LC-MS) (Thermo Scientific Exactive spectrometer), or TLC analysis (EM Science precoated silica gel 60 F_{254} plates). Visualization of TLCs was accomplished with a 254-nm UV light and by staining with a *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95 % EtOH) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of 0.1 % NaOH solution). Chromatography was performed on 40–63-μm silica gel (Silicycle) or on a Teledyne ISCO CombiFlash Rf. Melting points were determined using a Laboratory Devices Mel-Temp II and are not corrected. Infrared

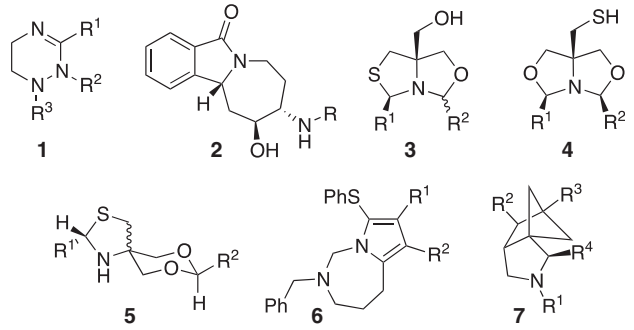
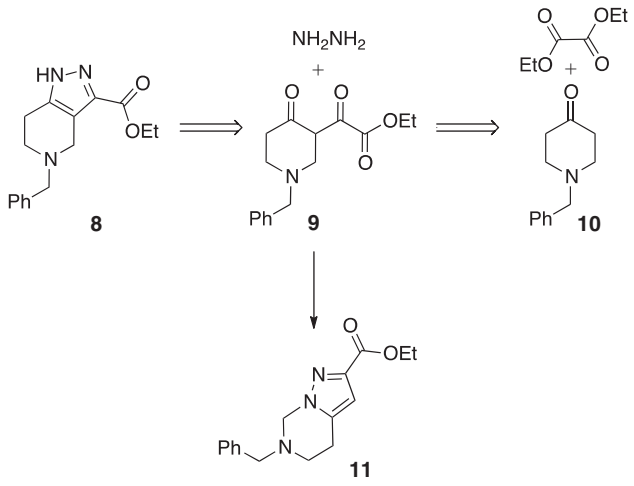
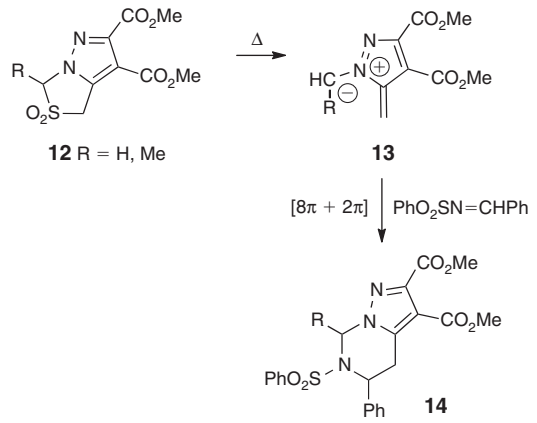


Fig. 1. Examples of new heterocyclic scaffolds resulting from cascade reactions.



Scheme 1. Unexpected formation of pyrazolopyrimidine **11**.



Scheme 2. Cycloaddition approach to pyrazolopyrimidine **14**.

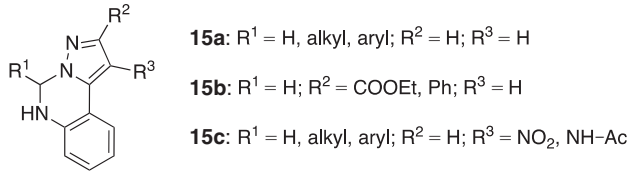


Fig. 2. Biologically active 5,6-dihydropyrazolo[1,5-*c*]quinazolines.

spectra were obtained on either a Nicolet Avatar 360, a Smiths Detection IdentifyIR Fourier-transform (FT)-IR spectrometer, or Perkin Elmer attenuated total reflection IR. Mass spectra were obtained on a high resolution LC-MS instrument (Thermo Scientific Exactive spectrometer; Waters XBridge™ BEH C18 2.5 µm, 2.1 × 50-mm column). All chiral compounds were formed as racemic mixtures. Purities were determined using an Agilent Technologies 385 evaporative light scattering detector. Microwave reactions were performed in a Biotage Initiator 2.0 microwave reactor. ^{1}H and ^{13}C NMR spectra were obtained on Bruker Avance 300, 400, 500-MHz instruments at room temperature unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) with the residual solvent peak used as an internal standard ($CHCl_3$ δ 7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C; DMSO δ 2.50 ppm for ^{1}H and 40.45 ppm for ^{13}C; CH_3OH δ 3.34 ppm for ^{1}H and 49.86 ppm for ^{13}C). ^{13}C NMR spectra were recorded using a proton-decoupled pulse sequence with d_1 of 2–5 s.

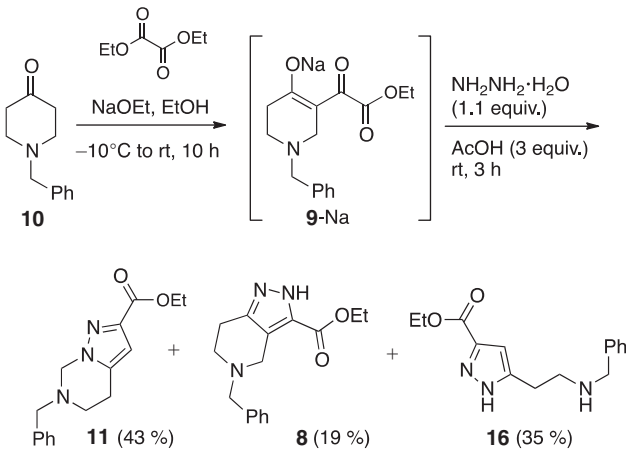
*Experimental Procedure for the Synthesis of 4,5,6,7-Tetrahydropyrazolo[1,5-c]pyrimidine **11***

Sodium (0.11 g, 4.7 mmol) was added to ice-cooled EtOH (15 mL) under a nitrogen atmosphere. After 2 h, the solution was further cooled to −10°C and diethyl oxalate (0.59 mL, 4.3 mmol) was added dropwise. *N*-Benzyl-piperidone (0.80 mL, 4.3 mmol) was added dropwise over 1 h. The mixture was warmed to room temperature (rt) and stirred for 10 h. The hydrazine monohydrate (0.23 mL, 4.7 mmol) was added and the mixture was stirred for 5 min. Then, pyridinium *p*-toluenesulfonate (PPTs) (2.2 g, 8.6 mmol, 2 equiv.) was added and the mixture was stirred for 5–6 h at rt. The reaction was monitored by LC-MS (gradient of 92 % water/0.1 % formic acid, 3 % acetonitrile/0.1 % formic acid/5 % MeOH to 2 % water/0.1 % formic acid, 93 % acetonitrile/0.1 % formic acid, 5 % MeOH). The reaction mixture was diluted with sat. $NaHCO_3$ (100 mL) and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by chromatography on SiO_2 (solid load, EtOAc/hexanes, 1 : 1, then EtOAc, and finally EtOAc/MeOH, 4 : 1) to give ethyl 6-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-*c*]pyrimidine-2-carboxylate **11** (0.77 g, 2.7 mmol, 62 %), ethyl 5-benzyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*c*]pyridine-3-carboxylate **8** (0.17 g, 0.60 mmol, 14 %), and ethyl 5-(2-(benzylamino)ethyl)-1*H*-pyrazole-3-carboxylate **16** (0.12 g, 0.44 mmol, 10 %) as viscous oils. Characterization data and ^{1}H and ^{13}C NMR spectra for these products and all new compounds are provided as Supplementary Material.

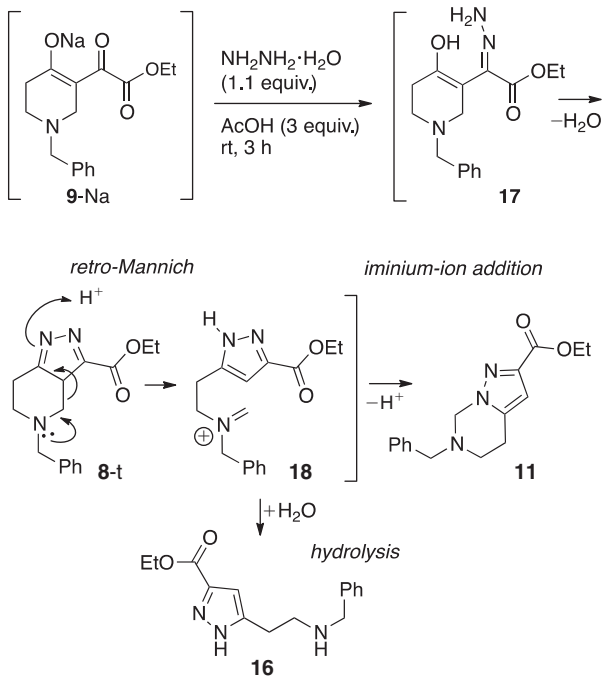
Results and Discussion

In an attempt to prepare pyrazolopyridine **8**, the commercially available piperidone **10** was treated with diethyl oxalate in the presence of sodium ethoxide in ethanol to afford the sodium salt of diketoester **9** (Scheme 3).[24] In order to avoid the isolation of polar intermediate **9**-Na, we treated the reaction mixture directly with hydrazine hydrate and acetic acid at room temperature for 3 h (Scheme 3). After workup and chromatographic purification, **11** was obtained in 43 % yield in addition to 19 % of the originally expected pyrazolopyridine **8** and ~35 % of the pyrazole amine **16**. The ^{1}H NMR and ^{13}C NMR spectra of **11** showed the presence of methylene protons (6.60 and 106.1 ppm respectively) that were inconsistent with structure **8**.

The isolation of pyrazole **16** suggested a possible reaction pathway involving a retro-Mannich fragmentation of pyrazolopyridine **8**-t to generate the pyrazolopyrimidine **11**



Scheme 3. One-pot synthesis of pyrazoles **8**, **11**, and **16**.

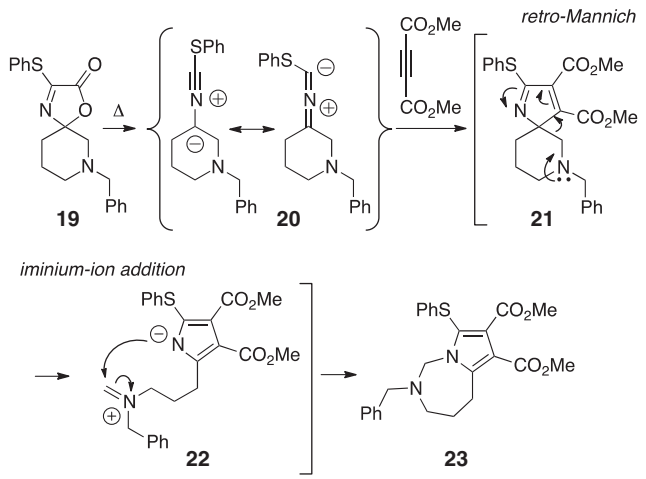


Scheme 4. Mechanistic hypothesis for the formation of **11** and **16**.

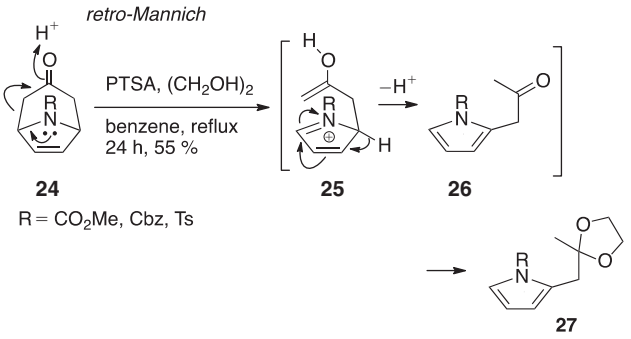
(Scheme 4).[25] Cyclization of hydrazone **17** leads to the expected **8** via its tautomer **8**-t; however, this compound can undergo a ring-opening retro-Mannich reaction to give iminium ion **18**. Hydrolysis of **18** results in the formation of the observed pyrazole side product **16**, whereas an addition reaction by the proximal pyrazole nitrogen leads to **11**. Interestingly, a similar reaction sequence was previously observed in our laboratory in the nitrile ylide cycloaddition with acetylenedicarboxylate (Scheme 5).[12]

Microwave heating of oxazolinone **19** generated the sulfur-stabilized nitrile ylide **20**, which underwent a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate to give 2*H*-pyrrole **21**, a tautomer that is isoelectronic with the key 4*H*-pyrazole **8**-t. The retro-Mannich reaction of the piperidine ring in intermediate **21** resulted in iminium ion **22**, which cyclized to give the seven-membered aminal **23**.

A related retro-Mannich process that is also in agreement with the reaction mechanism proposed in Scheme 4 was used to



Scheme 5. Formation of pyrrolodiazepine **23** by a piperidine retro-Mannich reaction.

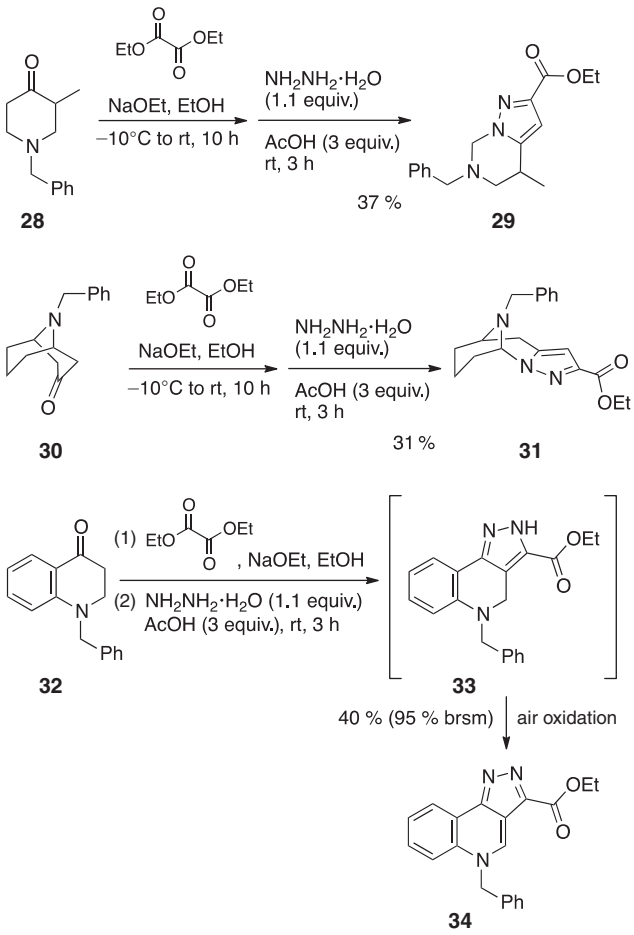


Scheme 6. Formation of pyrrole **27**.

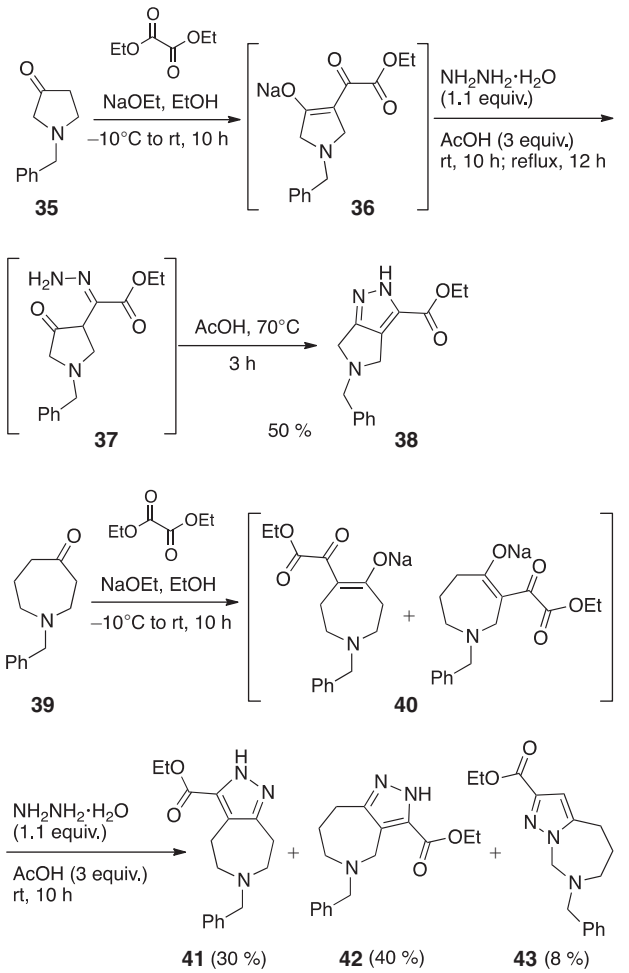
explain the isolation of **27** after treatment of tropenone **24** with ethylene glycol in the presence of catalytic amounts of *p*-toluenesulfonic acid (Scheme 6).[25j] The 2-alkylated pyrrole **27** was obtained as the major product after acetalization of the intermediate ketone **26**.

We investigated the scope of this new reaction by subjecting substrates **28**, **30**, and **32** to the reaction with diethyl oxalate and sodium ethoxide, followed by hydrazine in the presence of acetic acid (Scheme 7). Moderate yields of the retro-Mannich products **29** and **31** were obtained from the α-methylated piperidone **28** and the bicyclic ketone **30**, respectively, in addition to minor amounts of the corresponding pyrazolopyridines and unidentified side products that were not quantified. In contrast, treatment of the dihydroquinolone **32** under identical reaction conditions resulted in the exclusive formation of the pyrazoloquinoline **34** (95 % based on recovered **32**, 40 % isolated yield), presumably formed by air oxidation of the intermediate dihydroquinoline **33**. It is likely that the stabilization resulting from the conjugation of the pyrazole to the benzene ring, in addition to the inductive decrease in the electron density of the aniline nitrogen, prevents the retro-Mannich ring opening of **33** before oxidation to **34**.

We also evaluated the effect of the ring size in the β-aminoketone starting materials (Scheme 8). The five-membered substrate **35** underwent a smooth Claisen condensation with diethyl oxalate to give sodium salt **36**, but cyclocondensation with hydrazine was sluggish under the standard conditions and stopped at hydrazone **37**. More forcing conditions were necessary to convert **37** into the pyrrolopyrazole **38**; however, no



Scheme 7. Reaction scope with substituted *N*-benzylpiperidones. brsm: based on recovered starting material.



Scheme 8. Reaction scope of five- and seven-membered β-aminoketones.

retro-Mannich product was detected in the reaction mixture. Similarly, the seven-membered substrate **39** was converted into the regioisomeric mixture of sodium salts **40**, and although the subsequent conversion into the corresponding pyrazoles followed standard conditions, only a minor amount (8 %) of the retro-Mannich product, azepinopyrazole **43**, was isolated. Instead, the straightforward cyclocondensation products **41** and **42** were formed in high combined yield.

As an explanation of these results, we hypothesize that the retro-Mannich reaction requires the formation of an sp^3-hybridized ring carbon β to the amine (i.e. intermediate **8**-t). However, five- and seven-membered cycloalkanes have a stronger preference[26] for tautomers containing sp^2-hybridized carbons than the six-membered **8** and are therefore thought to be more resistant to the β-fragmentation process.

Based on the apparent need to stabilize tautomer **8**-t, or accelerate the pyrazole tautomerization from **8** to **8**-t while suppressing the hydrolysis of **18** (Scheme 4), we decided to revisit the formation of **11** in various acidic media (Table 1). Whereas the original protocol used 3 equiv. of acetic acid (entry 1), the reaction did not proceed in the absence of acid promotor and the sodium salt of β-diketone **9** was the sole product observed by LC-MS analysis (entry 2). In the presence of 1.2 equiv. of acetic acid (entry 3), both pyrazoles **11** and **8** were formed but yields were slightly reduced. Increasing the acetic acid content to 2 equiv. and adding sodium acetate as a buffer had a significant positive effect on the formation of the retro-Mannich reaction.

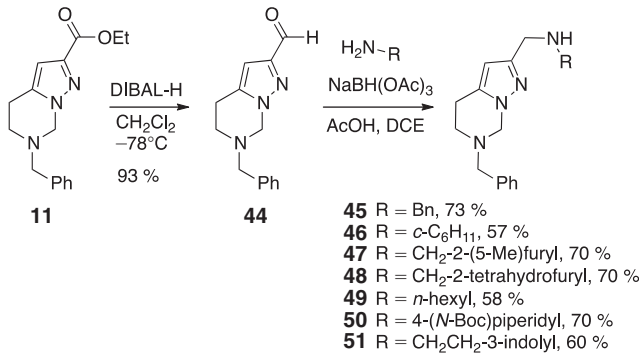
Table 1. Variation of acid promotor in the conversion of 9 into 8, 11, and 16 (Scheme 3)

Entry	Acid	Products (isolated yield)
1	AcOH (3 equiv.)	**11** (43 %), **8** (19 %), **16** (~35 %[A])
2	–	–[B]
3	AcOH (1.2 equiv.)	**11** (33 %), **8** (16 %), **16** (~30 %[A])
4	AcOH (2 equiv.), NaOAc (5 equiv.)	**11** (49 %), **8** (16 %), **16** (~20 %[A])
5	PPTs (2 equiv.)	**11** (62 %), **8** (14 %), **16** (~10 %[A])

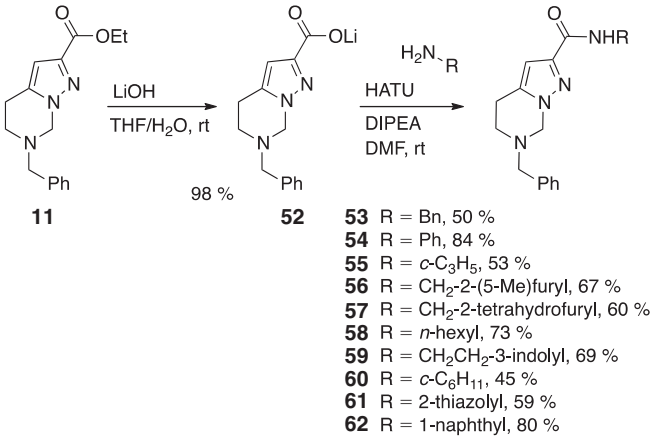
[A]Crude yield.
[B]The intermediate **9**-Na was the only compound observed by LC-MS.

Product **11** was now isolated in 49 % yield and increased selectivity over **8** and **16** (entry 4). In contrast, the use of stronger acids such as *p*-toluenesulfonic acid (TsOH), triflic acid, and Lewis acids such as BF_3–etherate led to general decomposition and only trace amounts of **11** (not shown). Pyridinium *p*-toluenesulfonate (2 equiv.) ultimately provided the best yield of the pyrazolopyrimidine **11** (62 %), with only 10–14 % of each of the side products **8** and **16** formed (entry 5).

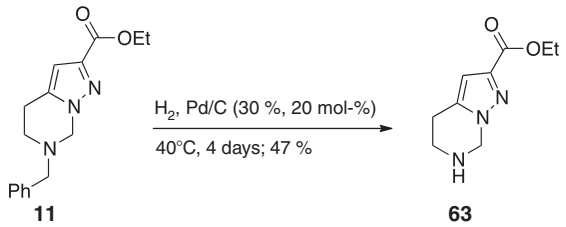
In spite of its aminal substructure, pyrazolopyrimidine **11** proved to be quite resistant to hydrolysis. A 0.7 mM test solution in phosphate buffered saline (PBS) at pH 7.3 did not show any



Scheme 9. Reductive aminations. DCE: 1,2-dichloroethane.



Scheme 10. Hydrolysis and amide formation.



Scheme 11. Reductive debenzylation of **11**.

degradation over 1 week monitoring by LC-MS. Therefore, we prepared a small library of analogues that could be used for biological screening purposes. Reduction of **11** to aldehyde **44** with diisobutylaluminium hydride (DIBAL-H) followed by reductive amination with $NaBH(OAc)_3$ led to amine derivatives **45**–**51** in 50–70 % overall yields (Scheme 9).

Amide derivatives of ethyl ester **11** were readily obtained by hydrolysis with LiOH in THF/H_2O and direct coupling of the resulting lithium salt **52** with primary aliphatic, aromatic, and heteroaromatic amines in the presence of the coupling agent (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*] pyridinium 3-oxid hexafluorophosphate) (HATU)[27] to give **53**–**62** in 45–84 % yield (Scheme 10).

Finally, we also explored the debenzylation of the scaffold **11** (Scheme 11). Although the reduction was sluggish, the free amine **63** was obtained in moderate yield by hydrogenolysis with Pd/C. Application of this procedure can provide a starting point for the preparation of additional analogues and library diversifications.

Conclusions

In the course of a standard conversion of β-diketone **9** to pyrazolopyridines, we found that six-membered fused pyrazoles such as **9** can rearrange to pyrazolopyrimidines **11** through a retro-Mannich reaction followed by an intramolecular aminal formation. The mechanistic subtleties of the retro-Mannich fragmentation currently limit this process to six-membered fused-ring systems among the five-, six-, and seven-membered heterocycles investigated here. In spite of the present limitation in scope, the substitution pattern of the pyrazolopyrimidines is well suited for further derivatization, as demonstrated in the generation of two small amine- and amide-based libraries. The resulting building blocks will likely be useful for future medicinal chemistry structure–activity relationship studies.

Supplementary Material

Experimental details, and ^{1}H and ^{13}C NMR spectra for all compounds are available on the Journal's website.

Acknowledgements

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