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First Copper-Catalyzed Intramolecular Amidation in Substituted 4-Iodopyrazoles Leading to the Synthesis of Pyrazolo[4,3-*b*]-pyridin-5-ones **

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Abstract: An unprecedented copper-catalyzed intramolecular amidation of substituted 4-iodopyrazoles generated either *via* Baylis–Hillman or Horner–Wadsworth–Emmons chemistry for the synthesis of pyrazolo[4,3-*b*]pyridine-5-ones is described. In addition, the effect of the stereochemistry of the acrylamide on the cross-coupling reaction has been investigated and it is demonstrated that only the Z-isomer is favoured to undergo the intramolecular cyclization.

Keywords: amidation; Baylis–Hillman reaction; C–N coupling; copper; Horner–Wadsworth–Emmons reaction; pyrazoles

Introduction

The pyrazole ring constitutes the substructural unit of an array of pharmacologically active compounds.[1] The syntheses of many of these derivatives are conveniently achieved from substituted halopyrazoles *via* cross-coupling as well as other halogen-metal exchange reactions.[2] In particular, substituted 4-iodopyrazoles, which can be easily synthesized,[3] are attractive substrates for such endeavours. But it is also known that iodine at the 4-position in pyrazole has a low order of reactivity.[4] In the context of our program aimed at demonstrating the synthetic applications of Baylis–Hillman derivatives for affording cyclic frameworks,[5] we have recently reported[6] a relatively fast Baylis–Hillman reaction of substituted 4-iodopyrazole-3-carbaldehyde. It was envisaged that adducts of this substrate can be effectively used as building blocks for the construction of pyrazole-annulated systems *via* intramolecular cross-coupling reactions. For example, the synthesis of pyrazolo[4,3-*b*]pyridine-5-one, which is the core unit of a Jun-N terminal kinase (JNK) inhibitor,[7] could be accomplished *via* a Cu-mediated Goldberg-type amidation of halides.[8] The retrosynthetic pathway delineated in Figure 1 outlines the strategy for this work.

Carbon-heteroatom bond formation by transition metal-catalyzed cross-coupling reactions is a standard technique used widely in synthetic organic chemistry. Although Pd-catalyzed[9] reactions have found broader applicability, Cu catalysts are preferred due to their low cost and easy handling procedures.[10] In this regard, work accomplished by several groups has shown that a combination of appropriate Cu salts, bases and ligands works efficiently for accomplishing the vast majority of aryl and heteroaryl C–N cross-coupling reactions.[11] Surprisingly, however, the recent compilations[1a,2b] covering the literature on cross-coupling reactions of pyrazoles reflected that most such endeavours using halopyrazoles were directed to generate a C–C bond. It is significant to note that C–N cross-coupling reactions in pyrazoles have been exemplified only by arylation of the ring nitrogen atom.[12] Literature pertaining to Cu-promoted amidation reveals that prior to the work by Dai and co-workers on microwave-assisted *N*-arylation of

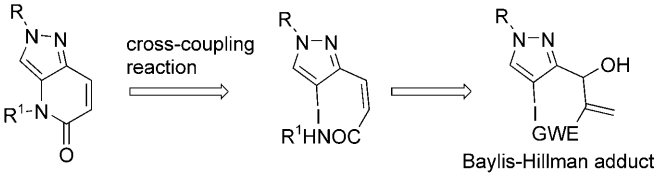


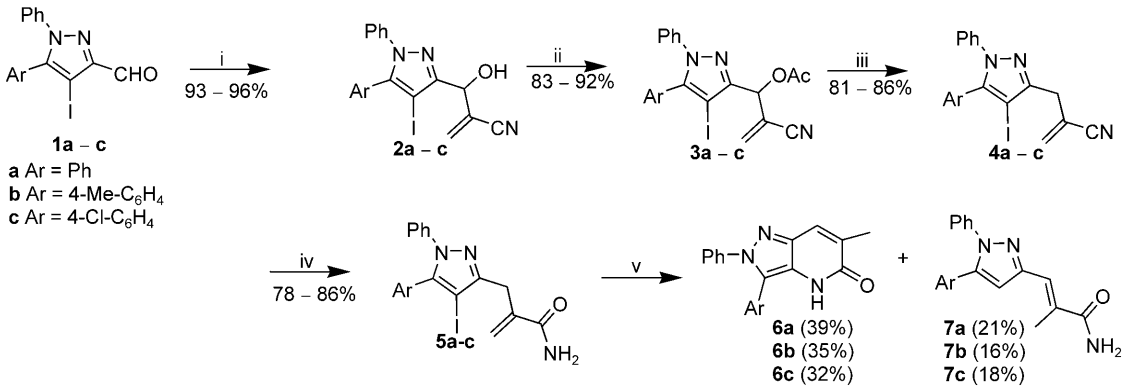
Figure 1. Retrosynthetic pathway for pyrazolo[4,3-*b*]pyridine-5-ones.

sterically hindered acyclic secondary amides, such reactions were restricted to primary amides, anilides and lactams.[13] Simultaneously, Hoogenband et al. also reported a Cu-mediated intramolecular amidation for the synthesis of *N*-substituted oxyindoles.[14] But, to the best of our knowledge, the amidation of 4-iodopyrazoles *via* cross-coupling reaction remains unreported. In our interest to demonstrate the synthetic applications of the Baylis–Hillman derivatives for heterocyclic synthesis, we embarked on a study to investigate the intramolecular amidation reaction in substituted 4-iodopyrazoles using Cu catalysts.

Results and Discussion

The objective of realizing the synthesis of an amide from the Baylis–Hillman adduct of 4-iodopyrazole-3-carbaldehyde was achieved following the procedure outlined in Scheme 1. Initial optimization was carried out with **1a**. The Baylis–Hillman reaction of **1a** with acrylonitrile yielded **2a** which upon acetylation produced the acetate **3a** (Scheme 1). The S_N2-displacement reaction of **3a** with $NaBH_4$ in the presence of DABCO in aqueous medium afforded **4a** which was hydrolyzed with TFA/H_2SO_4 to yield **5a**.[15] With the amide in hand we next investigated Buchwald's protocol for the Cu-mediated C–N cross-coupling reaction.[16] With the aim of optimizing the conditions, initially the reaction of **5a** with CuI was screened in the presence of several bases such as Cs_2CO_3, K_2CO_3, K_3PO_4 and ligands including ethylenediamine, *N*,*N*′-dimethylethylenediamine, phenanthroline, L-proline in DMF or dioxane (Table 1). Under all conditions two major spots were observed in the TLC analysis but the reaction was much cleaner with Cs_2CO_3 than with K_2CO_3 or K_3PO_4. These two products after isolation and spectroscopic characterization were identified as **6a** and **7a**. This exercise further revealed that the best yield of the desired product **6a** was achieved when the reaction was performed with CuI (0.2 equiv.) in the presence of Cs_2CO_3 (2 equiv.) as base and ethylenediamine (0.4 equiv.) as ligand in DMF at 100 °C (entry 3, Table 1). It was also observed that lowering the temperature increased the reaction time considerably. Beside CuI, we evaluated $CuBr_2$, CuCl and Cu_2O under similar conditions to affect the intended intramolecular cyclization. All these Cu salts successfully induced the cyclization reaction but the best yields of **6a** were achieved with CuI. It is significant to note that under all conditions formation of the annulated pyrazole was accompanied by the deiodinated product. However, it is worth mentioning that although the annulated pyrazole starts forming immediately, the presence of the deiodinated product becomes prominent only after 12 h of reaction time. Deiodination during the intramolecular amidation was in coherence with the observation of Dai et al.[13] The isomerization of the double bond to the endocyclic position in **6a** was attributed to the presence of base.[17] Notably, however, the ligandless reaction was found to be sluggish and the required product **6a** was isolated in traces only. Compounds **5b** and **c** prepared under conditions similar to **5a**, undergo the coupling reaction in identical conditions to yield **6b** and **c**, thereby indicating the general applicability of the protocol.

The successful formation of **6a–c** prompted us to investigate the scope of this approach by applying it to a variety of substituted acrylamides which were alternatively prepared from Baylis–Hillman adducts **8a–c** following the protocol displayed in Scheme 2. Acetylating **8a–c** with acetyl chloride gave **9a–c** in 87–91% yields. Treating **9a–c** with $NaBH_4$ in the presence of DABCO under aqueous conditions smoothly provided **10a–c** (82–87%). Saponification of **10a–c** with

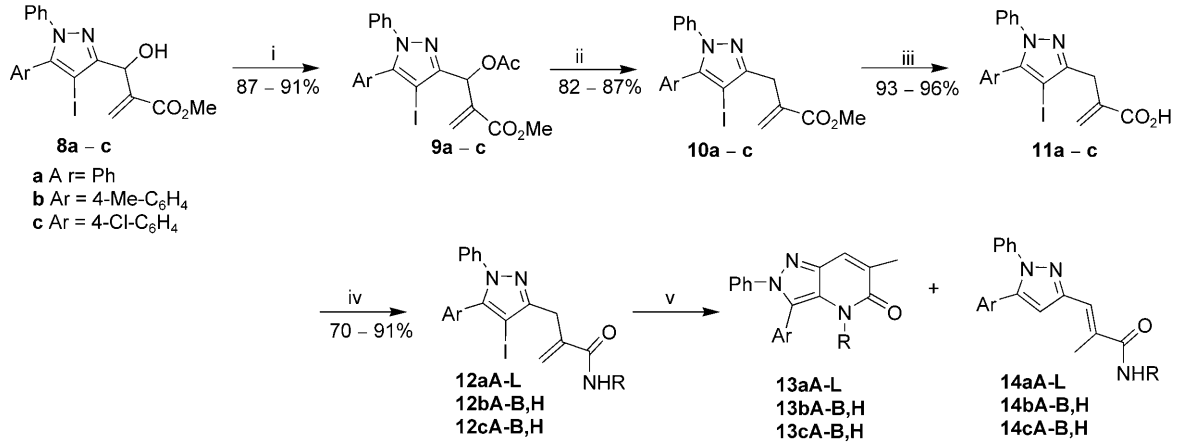


Scheme 1. *Reaction conditions:* i) Ref.[6] ii) AcCl (1.5 equiv.), pyridine (1.3 equiv.), CH_2Cl_2, 0 °C to room temperature, 2 h. iii) 1) DABCO (1 equiv.), THF-H_2O (1:1, v/v), room temperature, 15 min; iii) 2) $NaBH_4$ (1 equiv.), room temperature, 30 min. iv) TFA-H_2SO_4 (1:1, v/v), room temperature, 4 h. v) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 24 h.

Table 1. Optimization of the conditions for the intramolecular amidation with substrate **5a**.

Entry	Cu salt	mol%	Base	Ligand	Solvent	Time [h]	Isolated yields [%][a]	
							6a	**7a**
1	CuI	5	Cs_2CO_3	$NH_2(CH_2)_2NH_2$	DMF	96	18	39
2	CuI	10	Cs_2CO_3	$NH_2(CH_2)_2NH_2$	DMF	72	26	31
3	CuI	20	Cs_2CO_3	$NH_2(CH_2)_2NH_2$	DMF	24	45	21
4	CuI	20	Cs_2CO_3	$NH_2(CH_2)_2NH_2$	Dioxane	48	38	23
5	CuI	20	Cs_2CO_3	$MeNH(CH_2)_2NHMe$	DMF	24	30	18
6	CuI	20	Cs_2CO_3	1,10-phenanthroline	DMF	36	25	29
7	CuI	20	Cs_2CO_3	L-proline	DMF	36	22	24
8	CuI	20	K_2CO_3	$NH_2(CH_2)_2NH_2$	DMF	24	26	30
9	CuI	20	K_2CO_3	$MeNH(CH_2)_2NHMe$	DMF	36	24	18
10	CuI	20	K_2CO_3	1,10-phenanthroline	DMF	36	30	24
11	CuI	20	K_2CO_3	L-proline	DMF	36	9	38
12	CuI	20	K_3PO_4	$NH_2(CH_2)_2NH_2$	DMF	48	22	23
13	CuI	20	K_3PO_4	$MeNH(CH_2)_2NHMe$	DMF	48	16	25
14	CuI	20	K_3PO_4	1,10-phenanthroline	DMF	48	10	28
15	CuI	20	K_3PO_4	L-proline	DMF	48	6	26
16	$CuBr_2$	20	Cs_2CO_3	$NH_2(CH_2)_2NH_2$	DMF	24	38	35
17	CuCl	20	Cs_2CO_3	$NH_2(CH_2)_2NH_2$	DMF	36	30	28
18	Cu_2O	20	Cs_2CO_3	$NH_2(CH_2)_2NH_2$	DMF	24	19	31

[a] Reactions under several conditions showed multiple spots on TLC analysis.



Scheme 2. *Reactions conditions:* i) AcCl (1.5 equiv.), pyridine (1.3 equiv.), CH_2Cl_2, 0 °C to room temperature, 2 h. ii) 1) DABCO (1 equiv.), THF-H_2O (1:1, v/v), room temperature, 15 min; 2) $NaBH_4$ (1 equiv.), room temperature, 30 min. iii) Aqueous LiOH (5 equiv.), THF-MeOH, (5:1, v/v), room temperature, 5 h. iv) 1) DCC (1 equiv.), HOBt (1 equiv.), DMF, room temperature, 30 min; 2) RNH_2 (1.1 equiv.), 2 h. v) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 24 h.

LiOH yielded the corresponding acid **11a–c** in 93–96% as solids. The coupling reaction of **11a** with different aliphatic primary amines produced the required amides **12aA–G**. Fortunately, all acrylamides under optimized conditions for the intramolecular C–N coupling reaction resulted in a mixture of annulated derivative **13aA–G** and deiodinated product **14aA–G** (Table 2). Except for substrates **14aC**, **14aD** and **14aG** generated from *sec*-butylamine, cyclohexylamine and isopropylamine (entries 3, 4 and 7, Table 2), all compounds produced annulated pyrazoles in moderate yields. It has been already documented that the sterically hindered acyclic secondary amides furnish the cross-coupled product in low yields.[12,13] In order to settle the issue of the stereochemistry across the double bond in the deiodinated analogues, NOE experiments with a representative compound **14aE** were conducted. The results of this study showed the relative stereochemistry of the compound to be *E*. More amides **12aH–L** were prepared *via* coupling of acid **11a** with substituted anilines. Subjecting these amides (**12aH–L**) to CuI-promoted intramolecular coupling resulted in the formation of compounds **13aH–L** and the deiodinated products

Table 2. Yields[a] of compounds **12–14** afforded in Scheme 2.

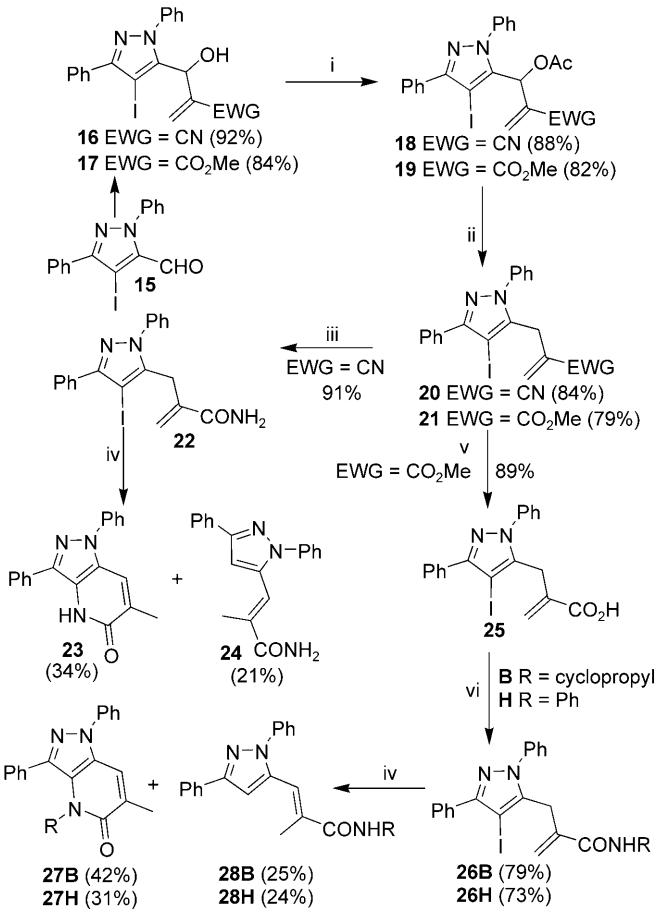
Entry	Compd no	Ar	R	**12**	**13**	**14**
1	**aA**	Ph	Bn	84	47	22
2	**aB**	Ph	cyclopropyl	78	57	21
3	**aC**	Ph	*sec*-butyl	76	10	47
4	**aD**	Ph	cyclohexyl	88	14	49
5	**aE**	Ph	$(CH_2)_2Ph$	91	38	31
6	**aF**	Ph	*n*-propyl	75	54	14
7	**aG**	Ph	isopropyl	83	21	43
8	**aH**	Ph	Ph	83	39	27
9	**aI**	Ph	4-Me-C_6H_4	79	62	22
10	**aJ**	Ph	4-OMe-C_6H_4	70	58	18
11	**aK**	Ph	3-Cl-C_6H_4	72	28	20
12	**aL**	Ph	4-Cl-C_6H_4	76	13	22
13	**bA**	4-Me-C_6H_4	Bn	81	57	24
14	**bB**	4-Me-C_6H_4	cyclopropyl	82	54	21
15	**bH**	4-Me-C_6H_4	Ph	78	33	23
16	**cA**	4-Cl-C_6H_4	Bn	85	46	33
17	**cB**	4-Cl-C_6H_4	cyclopropyl	73	50	28
18	**cH**	4-Cl-C_6H_4	Ph	72	37	19

[a] Isolated yields after column chromatography.

14aH–L. As can been seen from the entries in the Table 2, the nature of the substitution on the phenyl ring of the anilide influenced the formation of the cyclized product. The presence of electron-donating groups such as methoxy or methyl produced the annulated pyrazoles (**13aI–J**) in relatively better yields. In contrast, placing a mild electron-withdrawing group represented by chloro had a deleterious effect on the yield of the corresponding annulated products **(13aK–L)**.

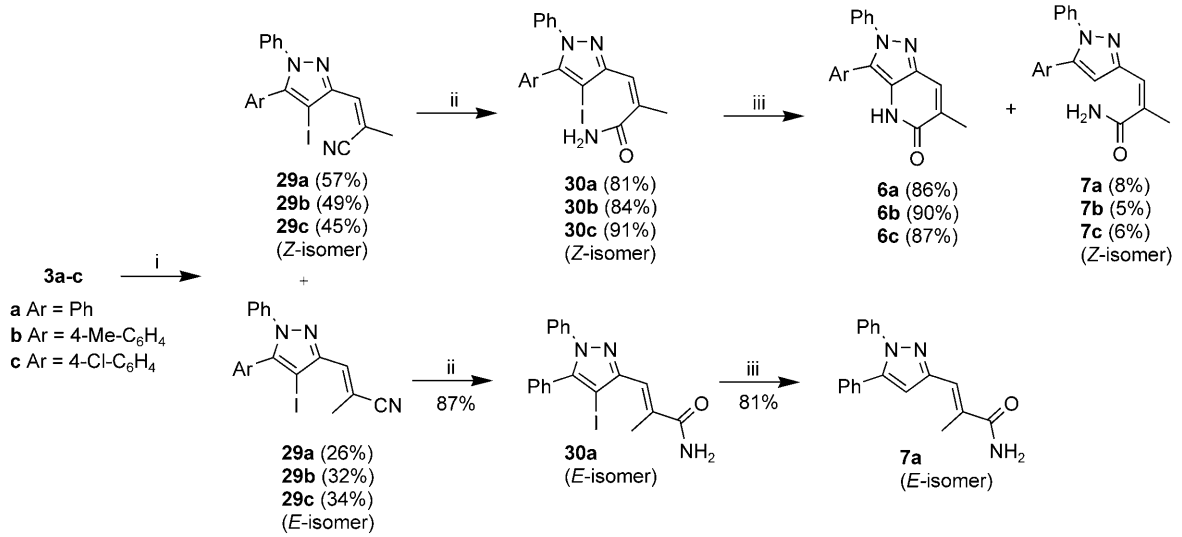
Next we prepared other amides **(12bA**, **B**, **H**, **12cA**, **B**, **H)** from acids **11b** and **c** to investigate whether substitution on the phenyl ring present at the 5-position of the pyrazole influences the outcome of the formation of product. Subjecting these amides to the Cu-mediated coupling reactions gave the required products **13bA**, **B**, **H** and **13cA**, **B**, **H** along with the deiodinated analogues **14bA**, **B**, **H** and **14cA**, **B**, **H**.

In order to enhance the diversity of annulated pyrazoles which could be accessed using the developed protocol, we next investigated couplings with the amides afforded from the Baylis–Hillman adducts (**16** and **17**) of 3-phenyl-4-iodo-5-pyrazole-carbaldehyde (**15**). In the first stage the primary amide **22** was synthesized from **16** *via* **18** and **20** as shown in Scheme 3. Treating it with CuI under the optimized condition resulted in a mixture from which 44% of annulated pyrazole **23** and 21% of deiodinated pyrazole **24** were isolated. Subsequently **26B** and **26H** were prepared from the Baylis–Hillman adduct **17** using the standard methodology. The CuI-mediated intramolecular C–N cross-coupling reaction in **26B** and **26H** resulted in a mixture from which the required products **27B** and **27H** and deiodinated analogues **28B** and **28H** were easily separated.



Scheme 3. *Reaction conditions:* i) AcCl (1.5 equiv.), pyridine (1.3 equiv.), CH_2Cl_2, 0 °C to room temperature, 2 h. ii) 1) DABCO (1 equiv.), THF-H_2O(1:1, v/v), room temperature, 15 min; 2) $NaBH_4$ (1 equiv.), room temperature, 30 min. iii) TFA-H_2SO_4 (1:1, v/v), room temperature, 4 h. iv) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 30 h. v) Aqueous LiOH (5 equiv.), THF-MeOH (5:1, v/v), room temperature, 5 h. vi) 1) DCC (1 equiv.), HOBt (1 equiv.), DMF, room temperature, 24 min; 2) RNH_2 (1.1 equiv.), 2 h.

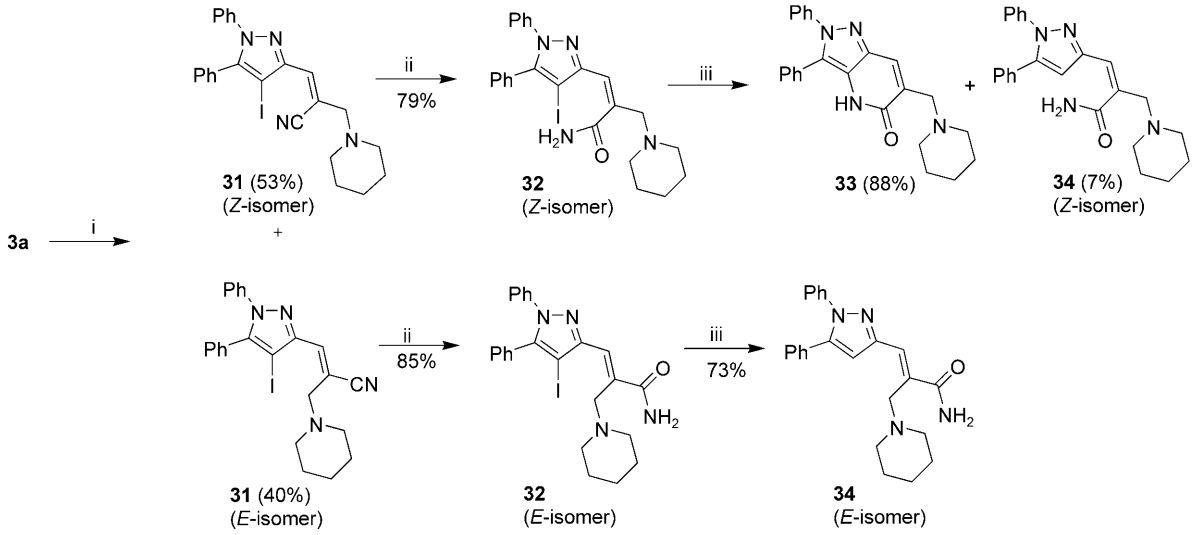
From results of the study at this stage it was apparent that the annulated pyrazoles were formed in moderate yields only and isomerization of the double bond accompanied by formation of deiodinated product bearing *E*-sterochemistry was common to all reactions. Mechanistic considerations generated interest in studying the fate of the C–N coupling in acrylamides with defined stereochemistry across the double bond. These amides were easily obtained from **3** as outlined in Scheme 4. Initially the reaction of **3a** with $NaBH_4$ in methanol afforded the alkene **29a** as a mixture of *E*- and *Z*-isomers which were readily separated *via* column chromatography. Acid hydrolysis in either isomers of **29a** produced the amide **30a** with retention of



Scheme 4. *Reaction conditions:* i) $NaBH_4$ (1.2 equiv.), MeOH, 0 °C, 20 min. ii) TFA-H_2SO_4 (1:1, v/v), room temperature, 6–8 h. iii) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 18 h [for **30** (*Z*-isomer)] and 24 h [for **30** (*E*-isomer)].

stereochemistry. It was pleasing to note that the coupling reaction of the Z-isomer of **30a** was relatively fast to furnish annulated pyrazole **6a** in 86% yield along with a minor amount of the Z-isomer of **7a** (8%). In contrast a similar reaction with the *E*-isomer of **30a** yielded the *E*-isomer of deiodinated pyrazole **7a** as the sole product. To further substantiate this outcome, either isomers of **30b** and **c** were prepared from **3b** and **c**. Gratifyingly, the C–N coupling with the Z-isomer of **30b** and **c** furnished **6b** and **c** in excellent yields. Small amounts of the *Z*-isomer of **7b** and **c** were also isolated.

It is documented that S_N2'-displacement reaction of the Baylis–Hillman acetate of acrylonitrile with an amine is diastereoselective in favour of the *Z*-isomer.[18] It was envisaged that such an allylamine would allow facile access to an amide with *Z*-stereochemistry and further enhance the scope of our strategy for obtaining annulated pyrazoles. Thus, in a representative study, treating **3a** with piperidine in methanol afforded **31** (Scheme 5). Unexpectedly **31** was formed as a mixture of *Z*- and *E*-isomers (57:43) which were separated. More importantly, however, hydrolysis followed by coupling reaction of the *Z*-isomer of **31** yielded the annulated derivative **33** in



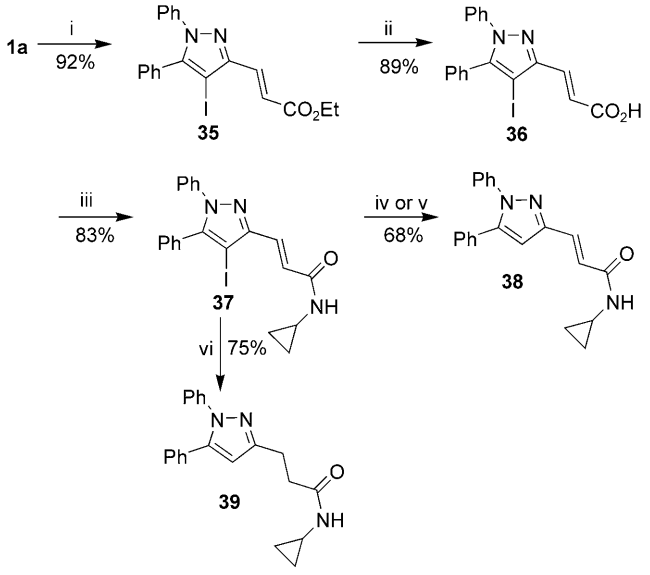
Scheme 5. *Reaction conditions:* i) Piperidine (1 equiv.), MeOH, room temperature, 1 h. ii) TFA-H_2SO_4 (1:1, v/v), room temperature, 8 h. iii) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 18 h [for **32** (*Z*-isomer)] and 24 h [for **32** (*E*-isomer)].

88% yield. On the other hand, the *E*-isomer of **32** reacted with CuI leading to **34** in 73% yield.

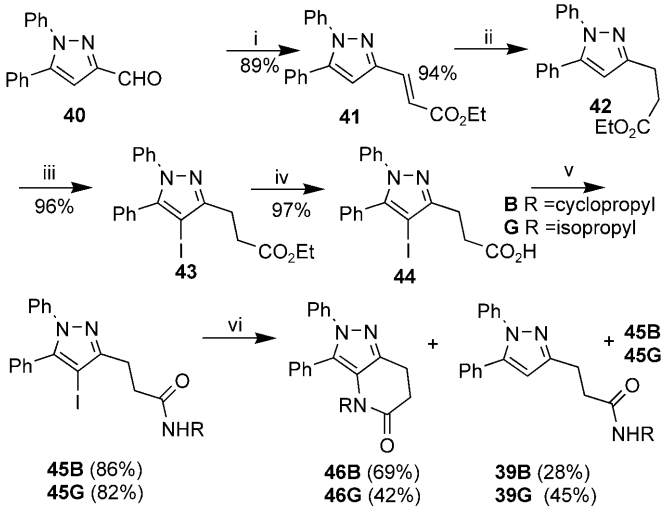
Having established the protocol with the Baylis–Hillman derivatives, we turned our attention to the acrylamide produced from the Wittig or Horner–Wardsworth–Emmons reaction of the 1,5-diphenyl-4-iodo-3-pyrazolecarbaldehyde. Treating **1a** with triethyl phosphonoacetate in the presence of NaH gave **35** that upon hydrolysis with LiOH yielded the acid **36** (Scheme 6). The stereochemistry was assigned as *trans* on the basis of coupling constants for the signal of protons across the double bond.[19] The coupling reaction of **36** with cyclopropylamine in the presence of DCC yielded the amide **37** in 83% yield. Expectedly, the attempted intramolecular cross-coupling reaction in this substrate produced the deiodinated product **38** in 68% yield exclusively.

This further substantiated the previous findings that the *E*-stereochemistry of the alkene is a limiting factor for the intramolecular cyclization. Nonetheless to establish the utility of our protocol for the development of annulated pyrazoles from this chemistry, we decided to reduce the double bond in the amide and then investigate the coupling reaction. In a representative study the reduction of the double bond in **37** was attempted under several conditions. The catalytic reduction with Pd on carbon or Et_3SiH-$PdCl_2$[20] resulted in the formation of deiodinated product **38** exclusively. However in the presence of Raney-Ni the deiodination of the pyrazole was accompanied by the reduction of the double bond to yield **39** in 75% yield.

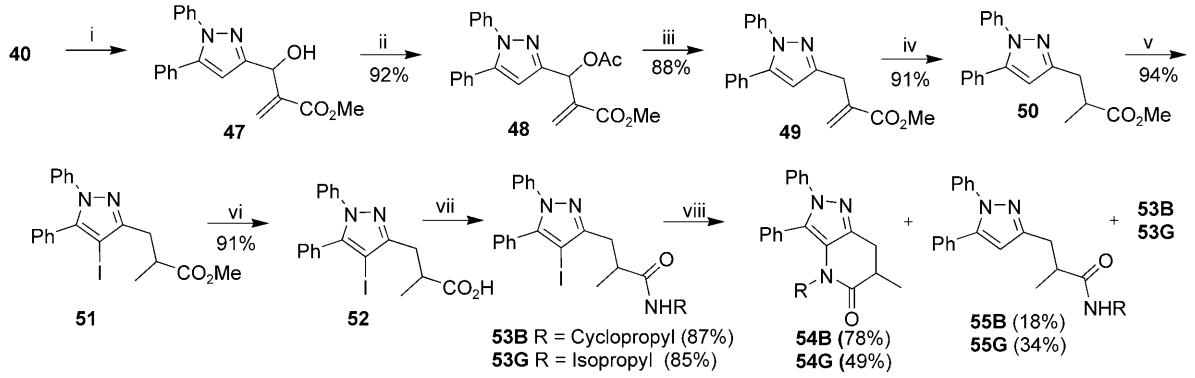
This failure prompted us to explore an alternative route for obtaining the required starting material. In this strategy it was decided to subject 1,5-diphenyl-3-pyrazolecarbaldehyde **(40)** to the Horner–Wadsworth–Emmon reaction initially, followed by reduction of the alkene and then perform the iodination reaction. Consequently, in a model study the aldehyde **40** was treated with triethyl phosphonoacetate to afford **41** which was subjected to hydrogenation in the presence of Raney-Ni in ethanol to yield **42** (Scheme 7). Iodinating **42** with ICl gave the iodinated pyrazole **43** in 96% yield, which was saponified in the presence of LiOH to furnish the acid **44** (97%). The coupling reaction of **44** either with cyclopropylamine or isopropylamine in the presence of isobutyl chloroformate and *N*-methylmorpholine (NMM) resulted in the formation of amide **45B** or **45G**. The CuI-mediated intramolecular amidation of these substrates were incomplete even after 48 h. Nevertheless, besides recovery of the starting material, we could successfully isolate the respective annulated pyrazoles **46B** and **G** and the deiodinated pyrazoles **39B** and **G** (**39B** is the same as **39**).



Scheme 6. *Reaction conditions:* i) $(EtO)_2POCH_2CO_2Et$ (1.5 equiv.), NaH (3 equiv.), THF, 0 °C to room temperature, 4 h. ii) Aqueous LiOH (5 equiv.), THF-MeOH (5:1, v/v), room temperature, 5 h. iii) 1) DCC (1 equiv.), HOBt (1 equiv.), DMF, room temperature, 30 min; 2) cyclopropylamine (1.1 equiv.), room temperature, 2 h. iv) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 24 h. v) Et_3SiH, $PdCl_2$, EtOH, room temperature, 24 h or Pd-C, H_2, 40 psi, 3 h. vi) Raney-Ni, H_2, MeOH, 40 psi, 3 h.



Scheme 7. *Reaction conditions:* i) $(EtO)_2P(O)CH{=}CO_2Et$ (1.5 equiv.), NaH (3 equiv.), THF, 0 °C to room temperature, 4 h. ii) Raney-Ni, H_2, EtOH, 40 psi, room temperature, 3 h. iii) ICl (3 equiv.), K_2CO_3 (3 equiv.), $CHCl_3$, room temperature, 10 h. iv) Aqueous LiOH (5 equiv.), THF-MeOH (5:1, v/v), room temperature, 5 h. v) 1) Isobutyl chloroformate (1.5 equiv.), NMM (1.5 equiv.), THF, −10 °C, 20 min; 2) RNH_2 (1.2 equiv.), −10 °C, 30 min. vi) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 48 h (yields of **46** and **39** are based on the consumed starting material).



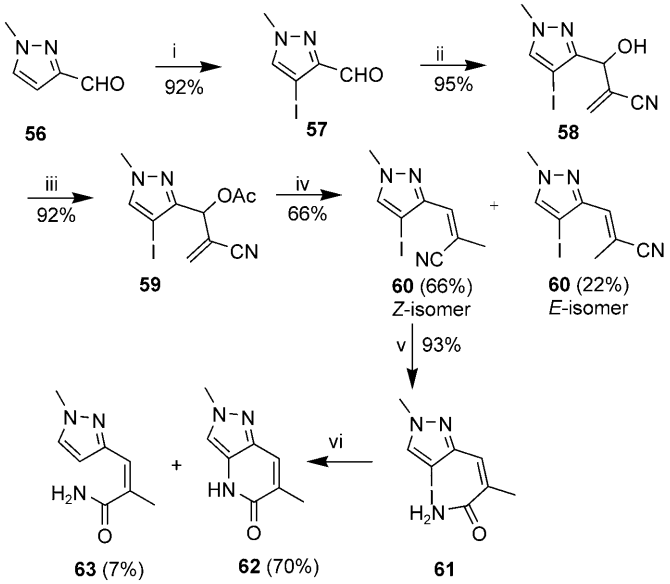
Scheme 8. *Reaction conditions:* i) Ref.[6] ii) AcCl (1.5 equiv.), pyridine (1.3 equiv.), CH_2Cl_2, 0 °C to room temperature, 2 h. iii) 1) DABCO (1 equiv.), THF-H_2O (1:1, v/v), room temperature, 15 min; 2) $NaBH_4$ (1 equiv.), room temperature, 30 min. iv) Raney-Ni, H_2, MeOH, 40 psi, room temperature, 3 h. v) ICl (3 equiv.), K_2CO_3 (3 equiv.), $CHCl_3$, room temperature, 12 h. vi) Aqueous LiOH (5 equiv.), THF-MeOH (5:1, v/v), room temperature, 5 h. vii) 1) Isobutyl chloroformate (1.5 equiv.), NMM (1.5 equiv.), THF, −10 °C, 15 min; 2) RNH_2 (1.2 equiv.), THF, −10 °C, 30 min. viii) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 48 h (yields of **54** and **55** are based on the consumed starting material).

Inspired by the outcome, we were prompted to apply this approach to similar substrates from the Baylis–Hillman chemistry. Hence, the Baylis–Hillman acetate **48** was synthetically manipulated to produce **52** as depicted in Scheme 8. Reaction of **52** with cyclopropylamine or isopropylamine in the standard conditions afforded the corresponding amides **53B** or **53G**. Similar to earlier observations with **45**, the coupling reactions of **53B** or **53G** were incomplete even after 48 h of reaction time. Importantly however, work-up and purification of the reaction mixture furnished the annulated pyrazoles **54B** and **54G** and deiodinated products **55B** and **55G** beside the starting material.

Finally, to investigate the necessity of the 5-aryl substituent, if any, for this chemistry we were prompted to examine the protocol with a pyrazole derivative wherein the 5-position remained unsubstituted. Accordingly, pyrazolecarbaldehyde **56** was generated starting from ethyl pyruvate.[21] Iodination of **56** followed by the Baylis–Hillman reaction with acrylonitrile afforded **58** in 95% yields (Scheme 9). Acetylation of **58** furnished the acetate **59** that reacted with $NaBH_4$ in methanol to afford acrylamide **60** as a mixture of *E*- and *Z*-isomers, in a 1:3 ratio. Separation of the isomers followed by sequential acid hydrolysis of the *Z*-isomer and Cu-mediated coupling reaction yielded the desired pyrazole **62** in 70% yield.

Conclusions

In conclusion, a Cu-mediated intramolecular amidation *via* C–N cross-coupling of the amide with the iodo group present at the 4-position in substituted pyrazoles to afford the annulated pyrazoles has been demonstrated for the first time. We have shown that this strategy successfully works for substrates derived either from the Baylis–Hillman or the Horner–Wadsworth–Horner chemistry. It has also been demonstrated that when an amide function is present across the double bond, only the *Z*-isomer has the capability to undergo intramolecular C–N coupling reactions. In contrast, the *E*-isomer of acrylamides afforded deiodinated pyrazoles as the sole products. Furthermore in the case of saturated amides the coupling reaction was found to be sluggish and is accompanied by deio-



Scheme 9. *Reaction conditions:* i) ICl (3 equiv.), K_2CO_3 (3 equiv.), $CHCl_3$, room temperature, 10 h. ii) CH_2=CHCN, (1.1 equiv.), DABCO (1 equiv.), room temperature, 4 h. iii) AcCl (1.5 equiv.), pyridine (1.3 equiv.), CH_2Cl_2, 0 °C to room temperature, 2 h. iv) $NaBH_4$ (1.2 equiv.), MeOH, room temperature, 20 min. v) TFA-H_2SO_4 (1:1, v/v), room temperature, 10 h. vi) CuI (0.2 equiv.), $NH_2(CH_2)_2NH_2$ (0.4 equiv.), Cs_2CO_3 (2 equiv.), DMF, 100 °C, 18 h.

dination of pyrazole. This simple and straightforward synthetic achievement updates the literature for C–N cross-coupling in 4-iodopyrazoles.

Experimental Section

General Procedure as Exemplified for the Synthesis of Compounds 6a and 7a from 5a

To a solution of amide **5a** (0.80 g, 1.86 mmol) in DMF (10 mL), Cs_2CO_3 (1.21 g, 3.73 mmol), CuI (0.071 g, 0.37 mmol) and ethylenediamine (50 μL, 0.74 mmol) were added and the reaction mixture was heated at 100 °C for 24 h under a nitrogen atmosphere. Thereafter, the solvent was removed under reduced pressure and the residue was taken up in ethyl acetate (40 mL) and washed with water (50 mL). The aqueous layer was further extracted with ethyl acetate (2×25 mL) and the collected organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Column chromatography of the crude product over silica gel furnished the pure annulated pyrazole **6a** as a white solid (ethyl acetate/hexanes, 3:10; yield: 0.25 g, 45%) and the deiodinated pyrazole **7a** also as a white solid (ethyl acetate/hexanes, 3:7; yield: 0.12 g, 21%).

6-Methyl-2,3-diphenyl-2,4-dihydro-5*H*-pyrazolo[4,3-b]pyridin-5-one (6a): mp 240–242 °C; $R_f = 0.31$ (ethyl acetate/hexanes, 2:3); IR (KBr): $\nu_{max} = 1611$ (C=N), 1654 (CONH), 3454 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.27$ (d, 3H, $J = 1.2$ Hz), 7.25–7.28 (m, 3H), 7.34–7.45 (m, 7H), 7.73 (d, 1H, $J = 1.2$ Hz), 9.31 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 17.9$, 123.6, 125.1, 125.6, 127.9, 128.8, 129.1, 129.2, 129.3, 132.3, 137.7, 139.8, 164.0; MS (ES+): $m/z = 302.3$ ($M^+ + 1$); anal. calcd. for $C_{19}H_{15}N_3O$ (exact mass: 301.1215): C 75.73, H 5.02, N 13.94; found: C 75.98, H 5.0, N 13.89.

(*E*)-3-(1,5-Diphenyl-1*H*-pyrazol-3-yl)-2-methylprop-2-enamide (7a): mp 123–124 °C; $R_f = 0.13$ (ethyl acetate/hexanes, 2:3); IR (KBr): $\nu_{max} = 1616$ (C=N), 1668 ($CONH_2$), 3417 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 2.35$ (d, 3H, $J = 1.1$ Hz), 5.94 (brs, 2H), 6.69 (s, 1H), 7.21–7.36 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 14.8$, 109.5, 125.2, 126.1, 127.8, 128.6, 128.8, 129.0, 130.2, 131.9, 139.9, 144.0, 148.8, 171.8; MS (ES+): $m/z = 304.2$ ($M^+ + 1$), 287.3 ($M^+ - 16$); anal. calcd. for $C_{19}H_{17}N_3O$ (exact mass: 303.1372): C 75.23, H 5.65, N 13.85; found: C 75.28, H 5.41, N 13.96.

Supporting Information

Preparations of all compounds along with their characterization data and copies of ^1H and ^{13}C NMR spectra are available in Supporting Information.

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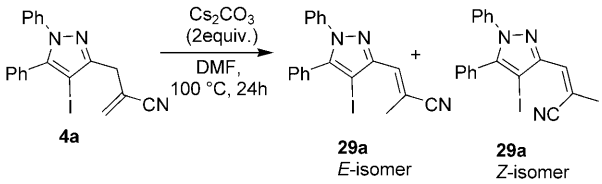

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