

A Simple and Versatile Protocol for the Preparation of 1,3-Functionalized Heterocycles Utilizing Benzoylpyruvates

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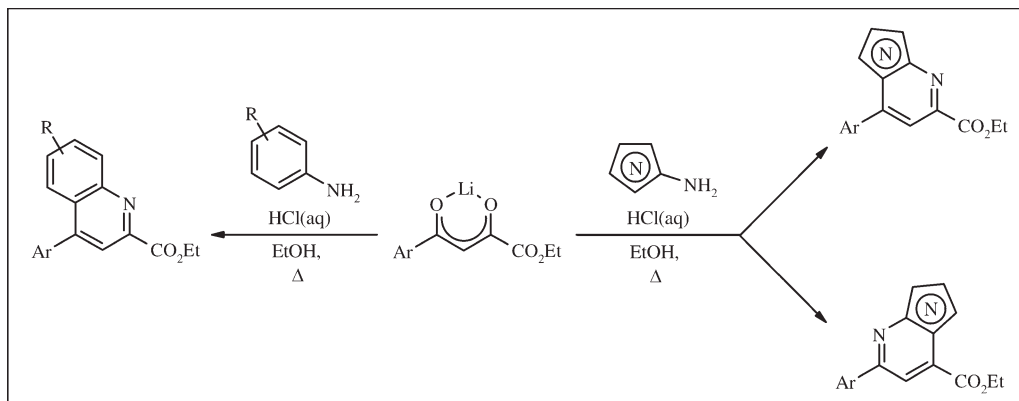
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Acid-mediated condensation between benzoylpyruvates and various dinucleophiles in alcoholic solvent furnished the heterocyclic imprint in moderate to good yield. Combining a range of symmetric as well as nonsymmetric nitrogen/nitrogen or nitrogen/carbon centered dinucleophiles resulted in excellent regioselectivity. γ -Difunctionalized fused pyrimidines, pyridazines, and pyridines were produced in this manner. The protocol was designed to obviate chromatographic purification.

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INTRODUCTION

Addition of ambivalent nitrogenous nucleophiles to β -diketones offers an attractive entry to the preparation of aromatic heterocyclic structures carrying distinct functional motifs. Acting as a template, the structural features of the β -diketone provide the central framework to be resonated in the resulting aza-heterocycle. We have in particular directed our attention towards the application of benzoylpyruvates **1** as the means to prepare pyridine and pyrimidine derivatives incorporating a γ -related aryl ester pattern.

From a pharmaceutical point of view, the spatial arrangement of substituents conferred on heterocycles via benzoylpyruvate chemistry is highly interesting, as it can give rise to pronounced biological activity. For example, pyrazoles, isoxazoles, pyrimidines, and pyridines carrying a γ -aryl carboxy motif are associated with such diverse effects as GPCR antagonism [1–4], ion-channel modulation [5], and kinase inhibition [6,7].

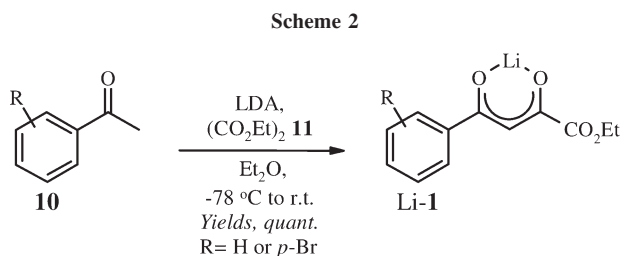
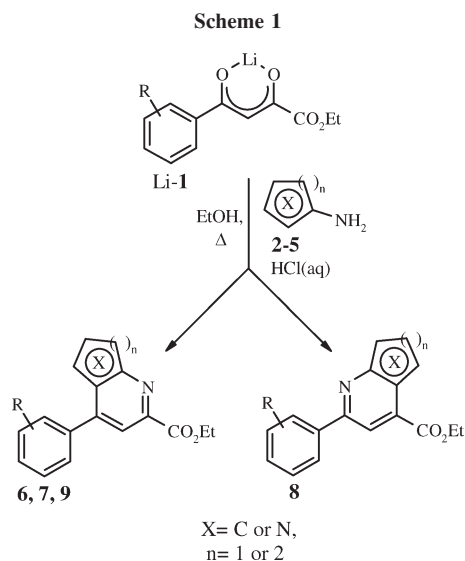
Herein, we want to report a convenient route for the preparation of novel γ -arylated aza-heterocyclic esters by highly chemo- and regioselective condensation of lithio benzoylpyruvate **1** with aromatic amines **2–5**

(Scheme 1). Considering the number of different benzoylpyruvates **1** readily available from commercial acetophenones **10**, this protocol can be seen as an alternative to arylation of the parent heterocycle via cross-coupling reactions. Indeed, the preparation of prerequisite substrate for the corresponding cross-coupling may be a nontrivial matter. In contrast, merited by the ease of execution, the delineated condensation strategy is amenable for parallel synthesis.

RESULTS AND DISCUSSION

As is expected for β -diketones lacking a mirror plane, the ambiphilic nature of benzoylpyruvates poses a potential regiochemical problem. However, in the latter case, the reactivity gets further complicated by the presence of the ester functionality. Although the ester functionality imparts the adjacent carbonyl with an augmented electron deficiency, it might itself undergo nucleophilic attack, thereby giving rise to a potential chemoselective problem as well (Fig. 1) [8].

In general, the stipulated benzoylpyruvate **1** can readily be accessed by reacting the metal enolate of the



corresponding acetophenone **10** with diethyl oxalate **11** [9–11]. In particular, owing to the excellent chelating ability of β -diketones, the *en route* lithium salt of benzoylpyruvate **1** can usually be isolated as a shelf-stable solid by simple filtration [11]. Thus, sequential treatment of **10** with LDA and diethyl oxalate **11** was the preferred method to prepare the needed starting material (Scheme 2). Initially, we opted for the *p*-Br-substituted benzoylpyruvate Li-**1** as a model compound, expecting it to be conducive in terms of product identification, based on its isotopic fingerprint (LC-MS) and crystallographic properties (X-ray). However, in some cases we found that the parent benzoylpyruvate Li-**1** (R = H) proved superior for crystallographic purposes.

Although the binding of lithium was beneficial with regard to the isolation of **1**, the chelated form proved to have an adverse effect on the cyclodehydration. Without *in situ* quenching of Li-**1**, concomitant retro-aldol reaction was observed on the application of any prospect dinucleophile in refluxing ethanol. Consequently, the initial attempts only returned acetophenone **10** as the breakdown product.

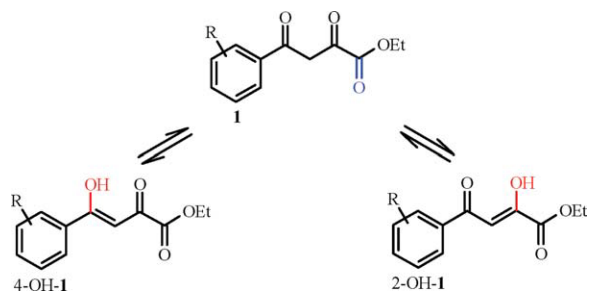


Figure 1. Tautomerism in benzoylpyruvates. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Gratifyingly, when first having treated Li-**1** with two equivalents of hydrochloric acid, subsequent cyclodehydration could be realized for a range of aromatic amines **2–5** *vide infra*. Furthermore, the reaction displayed a distinct regiochemical preference in each case.

In accordance with the delineated protocol, a selection of five-membered aza-heterocyclic amines **2** was reacted with Li-**1** to furnish the corresponding [a]-fused pyrimidines **6** (Scheme 3). However, the influence exerted by the individual N,N-dinucleophiles on the success of cyclodehydration implicated a dependency on the pK_a of the protonated parent heterocyclic system (Table 1). To expand upon the latter point, the pK_a -values of pyrazole, 1,3,4-triazole, and tetrazole are 2.5, 2.2, and –3.0, respectively [12,13], whereas the pK_a of imidazole is 7.0 [12]. This may provide an explanation for the failure of imidazole **2b** and benzimidazole **2f** to react under the given conditions.

By the means of single-crystal diffraction technique, it was subsequently possible to make an unambiguous regiochemical assignment of **6b** (Fig. 2), resulting from cyclodehydration with pyrazole **2a**. Curiously, a reversal of regiochemistry takes place when interchanging the ester moiety in Li-**1** for a CF_3 -group, *i.e.*, turning the system into a conventional β -diketone. Thus, applying a similar protocol as ours, Filyakova *et al.* have reported on the preparation of an analogous 5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine, which was verified by crystallography [14]. The two opposing results indicate the ability of the ester to act as regiochemical handle (*vide infra*).

With respect to regiochemistry, the fused system obtained through condensation of tetrazole **2d** posed the intriguing possibility of valence tautomerism [15]. At the outset, it was expected that the initially formed tetrazolo[1,5-*a*]pyrimidines **6f** and **6g** could undergo

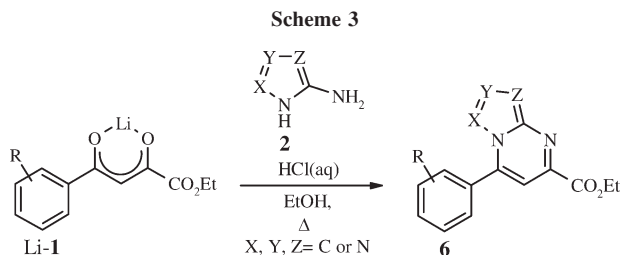


Table 1
Synthesis of [a]-fused pyrimidines **6**.^a

Entry	Product	R	Aryl amine	Time (h) ^c	Yield (%) ^d
1	6a	<i>p</i> -Br	1H-Pyrazol-5-yl 2a	13	75
2	6b	H	1H-Pyrazol-5-yl 2a	13	69
3	6c	<i>p</i> -Br	1H-Imidazol-5-yl 2b	96 ^e	n.r.
4	6d	<i>p</i> -Br	1H-1,2,4-Triazol-5-yl 2c	48	73
5	6e	H	1H-1,2,4-Triazol-5-yl 2c	48	70
6	6f^b	<i>p</i> -Br	1H-Tetrazol-5-yl 2d	13	79
7	6g^b	H	1H-Tetrazol-5-yl 2d	13	68
8	6h	<i>p</i> -Br	2H-Indazol-3-yl 2e	13	85
9	6i	H	2H-Indazol-3-yl 2e	13	87
10	6j	<i>p</i> -Br	1H-Benzimidazol-2-yl 2f	96 ^e	n.r.

^a The reactions were performed with equimolar proportions of Li-1 and amine **2** in the presence of 2 equiv. of HCl (aq).

^b Interconverts to the corresponding azide **12**.

^c Time to achieve full conversion according to HPLC and LC-MS.

^d Isolated yield.

^e Experiment was terminated at the time indicated as no reaction had occurred.

equilibration to 2-azidopyrimidines **12f, g** (Fig. 3). However, the “pseudo symmetry” of **12f, g** would then obliterate the existing regiochemical preference via the erosive interconversion to **13f, g**. Subsequently, it was indeed demonstrated by the application of X-ray crystallography that in the solid state the tentatively assigned structure of fused tetrazole **6f** actually was 2-azidopyrimidine **12f** (Fig. 4).

Having established the feasibility of cyclodehydration on Li-1 utilizing selected N,N-dinucleophiles, the focus of the protocol was aimed at fusion with other types of five-membered aza-heterocyclic amines, *i.e.*, prospective C,N-dinucleophiles. Following this line of reasoning, Li-1 was allowed to react with N-amino heterocycles **3** to provide [b]-fused pyridazines **7** (Scheme 4). In the selected cases, the observed regiochemistry corresponded to the results obtained with aryl amines **2**. Here, however, the degree of aza-functionalization had a dramatic influence on the efficiency, with regard to product formation (Table 2).

Five-membered aza-heterocycles with an encased ethylene amine motif could in principle be rendered opera-

tional C,N-dinucleophiles via blocking or replacing the active ring-nitrogen. Hence, it was envisioned that the “aniline-type” aryl amines **4** would furnish [b]-fused pyridines. Although the primary projection was correct, the regiochemistry was at variance with the preceding examples. Thus, when Li-1 was reacted with C,N-dinucleophiles **4**, the resultant cyclodehydration provided the [b]-fused pyridine **8** (Scheme 5).

Applied on the product originating from condensation between Li-1 (R = H) and “enamine” **4a**, X-ray crystallography provided the conclusive structural information, showing **8b** to be the resulting regioisomer (Fig. 5).

Though, seemingly contradictory, with regard to benzoylpyruvate **1**, the sequence of addition leading to the different fused systems could well be the same (*vide supra*). Instead, it was surmised that the origin of regiochemical divergence resided on the nature of the applied dinucleophile. Depending on the hard/soft character of the aryl amine, in analogy with enamines, either the interconnected nitrogen or carbon could take precedence in the cyclodehydration. However, it also became clear

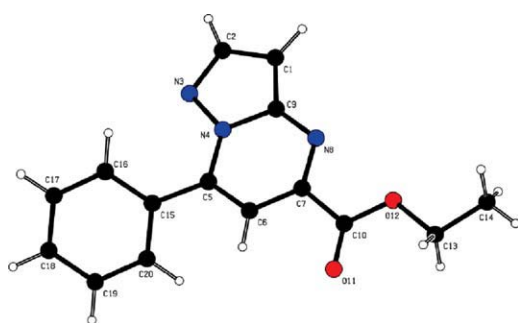


Figure 2. Crystal structure of compound **6b** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

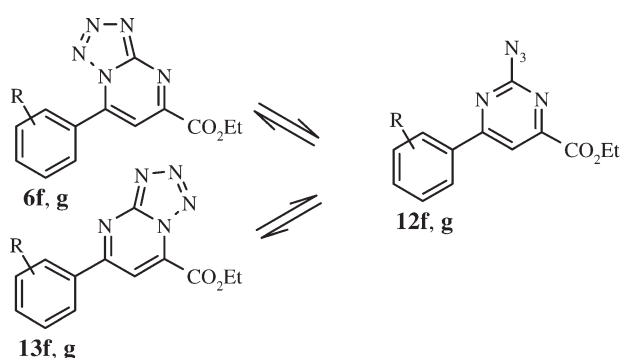


Figure 3. Valence tautomerism in tetrazolo[1,5-a]pyrimidine **6f** and **6g**.

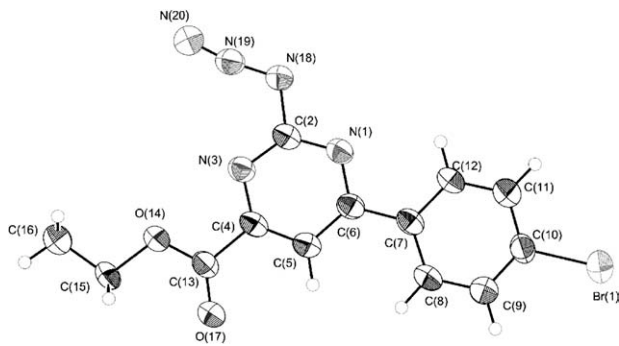


Figure 4. ORTEP presentation of compound 12f.

that the choice of C,N-dinucleophiles **4** was rather limited (Table 3).

By extending the ensemble of C,N-dinucleophiles to six-membered aryl amines **5**, *i.e.*, *bona fide* anilines, it was anticipated that the regiochemistry would realign with the initially observed preference to provide [*b*]-fused pyridines **9** (Scheme 6). However, if the underlying assumption regarding the regiochemical preference of benzoylpyruvate **1** proved correct, the resulting quinolines **9** would have the reversed structure compared with the Skrap–Doebner–von Miller protocol [15].

Upon reacting Li-1 with anilines **5**, it became evident that cyclodehydration could only be achieved when strongly electron donating substituents were present on the aryl moiety of the prospective C,N-dinucleophile (Table 4). The interplay of electronic properties is however more subtle than what might initially be gleaned from the reaction scheme. Thus, when Li-1 was treated

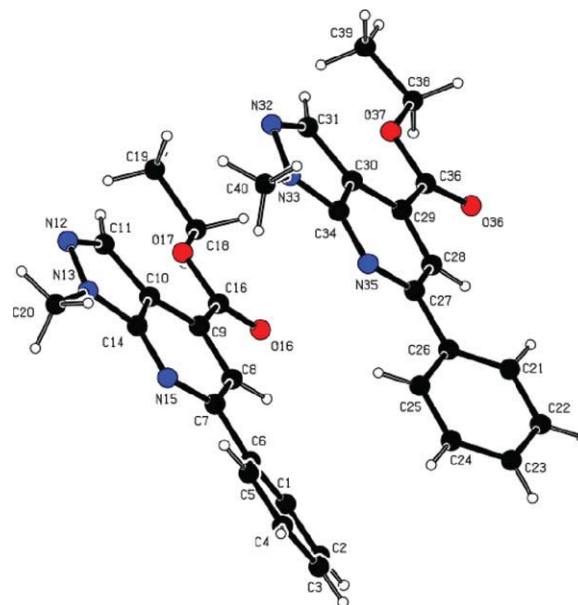


Figure 5. Crystal structure of compound 8b determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

with 4-amino-1H-indole **5d**, cyclization proceeded smoothly (entry 8 and 9). While, in contrast, the reaction with 6-amino-1H-indole **5e** was exceedingly sluggish (entry 11). Yet in both instances, the position *ortho* to the aniline functionality is activated by an indole nitrogen (Fig. 6).

Another aspect of the 4-amino-1H-indole derivatives **9f** and **9g** is the comprehensive prototropic tautomerism available to the fused rings. Thus, in the pertinent case, ¹H NMR indicates that the extended 14 π -electron system

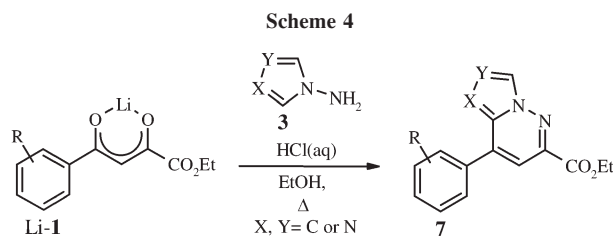


Table 2
Synthesis of [*b*]-fused pyridazines **7**.^a

Entry	Product	R	Aryl amine	Time (h) ^b	Yield (%) ^c
1	7a	<i>p</i> -Br	Pyrrol-1-yl 3a	0.5	85
2	7b	H	Pyrrol-1-yl 3a	0.5	79
3	7c	<i>p</i> -Br	1,2,4-Triazol-4-yl 3b	120	71
4	7d	H	1,2,4-Triazol-4-yl 3b	120	65

^a The reactions were performed with equimolar proportions of Li-1 and amine **3** in the presence of 2 equiv. of HCl (aq).

^b Time to achieve full conversion HPLC or LC-MS.

^c Isolated yield.

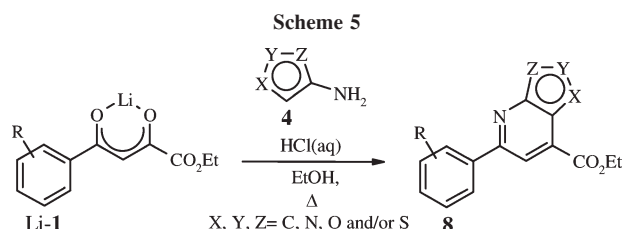


Table 3
Synthesis of [*b*]-fused pyridines **8**.^a

Entry	Product	R	Aryl amine	Time (h) ^b	Yield (%) ^c
1	8a	<i>p</i> -Br	2-Methyl-2H-pyrazol-3-yl 4a	120	70
2	8b	H	2-Methyl-2H-pyrazol-3-yl 4a	120	70
3	8c	<i>p</i> -Br	5-Methylisoxazole-3-yl 4b	120	n.r.
4	8d	<i>p</i> -Br	3-Methylisothiazol-5-yl 4c	120	n.r.

^a The reactions were performed with equimolar proportions of Li-1 and amine **4** in the presence of 2 equiv. of HCl (aq).

^b Time to achieve full conversion.

^c Isolated yield.

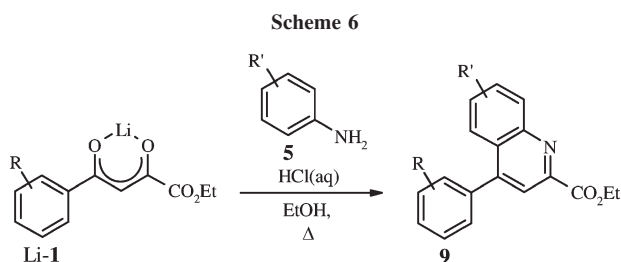


Table 4
Synthesis of [b]-fused pyridines **9**.^a

Entry	Product	R	Aryl amine	Time (h) ^b	Yield (%) ^c
1	9a	<i>p</i> -Br	3-Methoxy-phenyl 5a	120	n.r.
2	9b	<i>p</i> -Br	3,5-Dimethoxy-phenyl 5b	13	82
3	9c	H	3,5-Dimethoxy-phenyl 5b	13	73
4	9d	<i>p</i> -Br	3-(Dimethylamino)-phenyl 5c	13	90
5	9e	H	3-(Dimethylamino)-phenyl 5c	13	72
6	9f	<i>p</i> -Br	1H-Indol-4-yl 5d	13	25 ^d
7	9g	H	1H-Indol-4-yl 5d	13	23 ^d
8	9h	<i>p</i> -Br	1H-Indol-6-yl 5e	n.d.	n.d.
9	9i	H	1H-Indol-6-yl 5e	120	28 ^d

^aThe reactions were performed with equimolar proportions of Li-1 and amine **5** in the presence of 2 equiv. of HCl (aq).

^bTime to achieve full conversion or no further reaction occurred by HPLC or LC-MS.

^cIsolated yield.

^dPreparative HPLC due to instability.

behaves less aromatic than anticipated. The repositioning of the active proton also involves carbon prototropes and the only specie observed by NMR-spectroscopy was attributed to the 4H-tautomer (Fig. 7). This behavior probably reflects the “quinone-like” nature of the compound.

By comparison, the linear isomer **9i** resulting from condensation of Li-1 (R = H) with 6-amino-1H-indole **5e** behaves more like an aromatic 14 π -electron system and prototropic tautomerism is less pronounced. However, in general the quinolines **9** were less stable than the previous classes of cyclodehydration products **6**, **7**, and **8**.

With regard to the identity of the resulting compounds, we once again resolved to address the issue of regiochemical preference by capitalizing on X-ray crystallography. Applied to the cyclodehydration of Li-1 (R = Br) with 3-(*N,N*-dimethylamino)aniline **5d**, the structure was shown to be **9d** (Fig. 8). Thus, the condensation between benzoylpyruvates **1** and anilines **5** provide verily regioisomeric quinolines not attainable via the classic Skraup–Doebner–von Miller procedure [15].

CALCULATIONS

In the light of some contrasting findings published by Filyakova *et al.* regarding condensation on selected β -

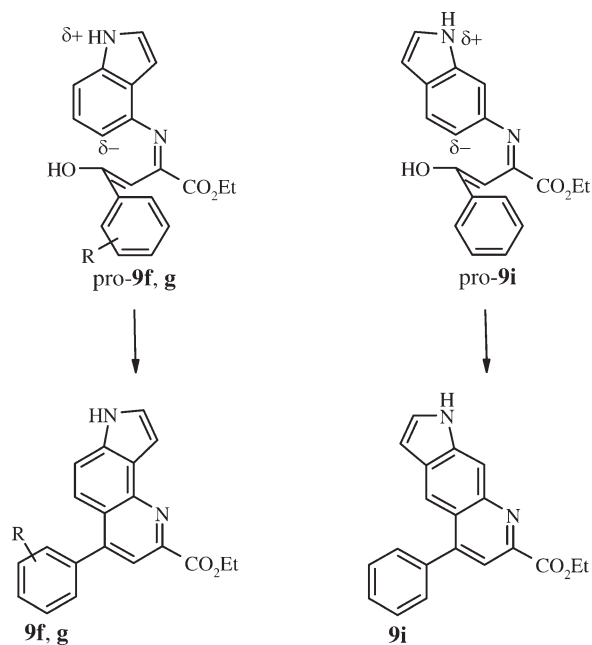


Figure 6. Tricycles resulting from condensation with 4-amino-1H-indole **5e** and 6-amino-1H-indole **5f**.

diketones [14], we wanted to make a side-by-side comparison with benzoylpyruvate **1**, applying high-level QM calculations to gain insight into the origin of the observed regio-divergence.

Discounting the reactive nature of the ester moiety, a cursory inspection of benzoylpyruvate **1** might pin down the system as merely a benzoylacetone with an electron withdrawing group append to its terminus. Indeed from

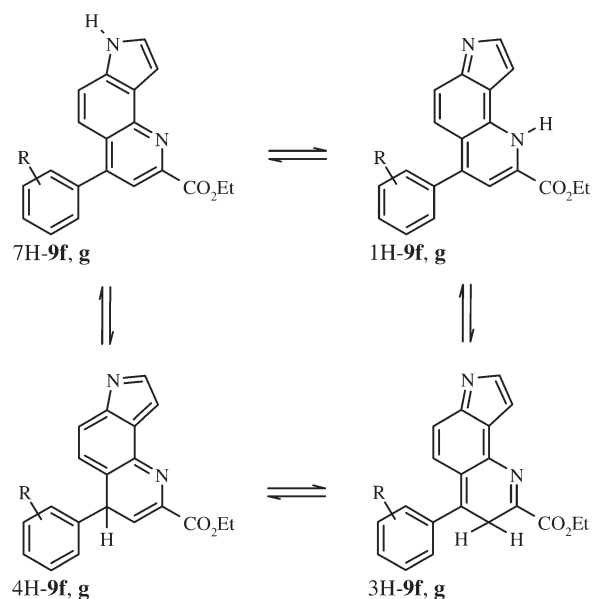


Figure 7. Tautomerism in pyrrolo[2,3-h]quinolines **9f** and **9g**.

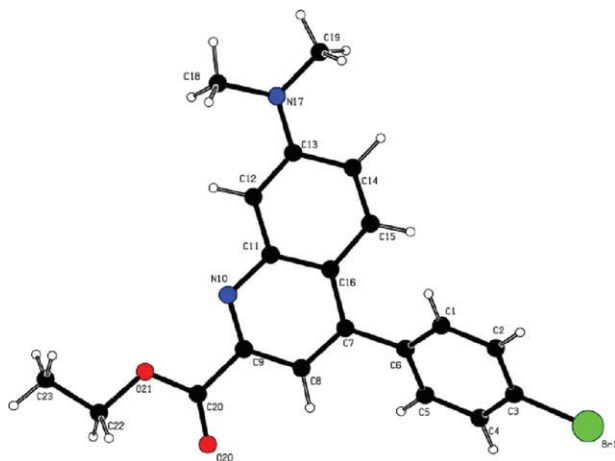


Figure 8. Crystal structure of compound **9d** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

this vantage point, benzoylpyruvate **1** compares well with the fluorinated β -diketone **14** used by Filyakova *et al.* [14]. Thus, in both cases, the keto-functionalities might be projected to exhibit “pseudo-degenerate” behavior (Fig. 9). As an initial conjecture, one would consequently expect cyclodehydration on benzoylpyruvate **1** and fluorinated β -diketone **14** to give rise to similar regioselectivity. Indeed, our calculations on the relative energies of protonated β -diketone **14** only differ with 0.3 kcal/mol for the two positions. This is within the error margin of the applied method [16].

Taking into account, the participation of the ester moiety in benzoylpyruvate **1** alters the picture dramatically: The ability of the ester function to act as a hydrogen bond acceptor facilitates formation of a five-membered chelate with the adjacent carbonyl. According to the performed calculations, using methyl derivative **15** as a model compound, the individual protonated forms of the β -diketo system alone are energetically comparable. However, when the protonated forms involving a five-membered chelate are introduced, the energy of the system is markedly lower by 2.6 and 3.2 kcal/mol, respectively (Fig. 10) [16,17]. Thus, these calculations lend support to the hypothesis that the ester moiety in benzoylpyruvate **1** may serve as a regiochemical handle.

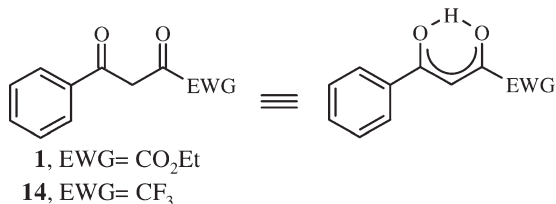


Figure 9. Pseudo-degenerate nature of the β -diketo system.

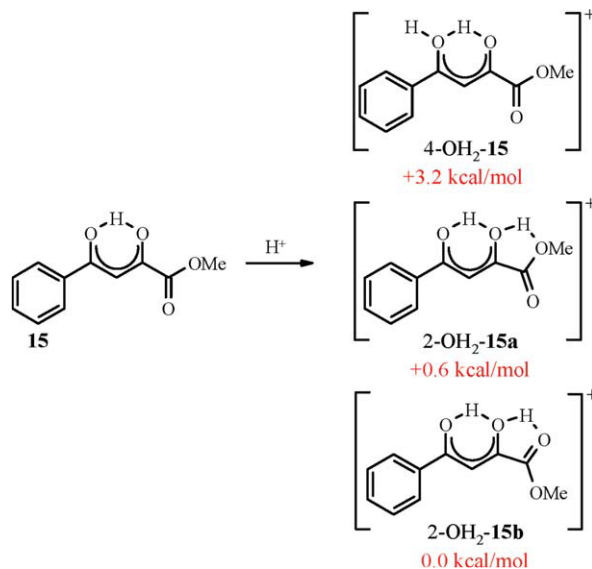


Figure 10. Calculated relative energies of protonated model benzoylpyruvate **15** based on B3LYP/6-31G**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

CRYSTALLOGRAPHY

Data collection, structure solution, and refinement. Diffraction data for (**6b**), (**8b**), (**9f**), and (**12a**) were collected at 200(2) K using either a Nonius Kappa-CCD or a Bruker APEX-II CCD diffractometer with graphite-monochromated Mo K α radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods and refined with F^2 against all reflections. All but one had one molecule in the asymmetric unit, which for **8b** contained two crystallographically unique molecules. Figures 2–5 and 8 show the molecular conformation, with the atom-labeling schemes. Compounds **6b**, **8b**, **9d**, and **12a** do not contain H-bond donor atoms and consequently do not form classical H-bonds [18].

CONCLUSIONS

This article outlines a simple and versatile approach to furnish fused heterocycles grafted on the benzoylpyruvate backbone. Depending on the nature of the applied dinucleophilic class, an alternation of regiochemistry could be observed. However, in each case the process was highly regioselective. At the basis of the observed selectivity, we postulate the participation of the ester portion in benzoylpyruvates as a decisive factor.

EXPERIMENTAL

NMR spectra were recorded either on a Bruker DPX400 NMR spectrometer operating at 400 MHz for ¹H, and 101 MHz for ¹³C equipped with a four-nucleus probe-head with Z-gradients, or a Bruker Avance III 500 NMR spectrometer, operating at 500 MHz for ¹H and 126 MHz for ¹³C equipped

with a 5mm TCI cryo probe-head with Z-gradients. Chemical shifts are given in ppm down- and upfield from tetramethylsilane (0.00 ppm). DMSO- d_6 δ_H 2.49; δ_C 39.51 and $CDCl_3$ δ_H 7.27; δ_C 77.00 were used as reference signals. All experiments were performed at a sample temperature of $26^\circ C \pm 2^\circ C$. LC-MS analyses were performed on a LC-MS system consisting of a Waters Alliance 2795 HPLC, a Waters PDA 2996 diode array detector, a Sedex 75 ELS detector, and a ZQ 2000 single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in positive and negative ion mode. The capillary voltage was set to 3.3 kV and the cone voltage to 28 V, respectively. The mass spectrometer was scanned between m/z 100–700 with a scan time of 0.3 s. The diode array detector scanned from 200–400 nm. The temperature of the ELS detector was adjusted to $40^\circ C$ and the pressure was set to 1.9 bar. Separation was performed on Gemini C18 3.0×50 , $3 \mu m$ (Phenomenex) run at a flow rate of 1 mL/min. A linear gradient was applied starting at 100% A (A: 10 mM ammonium acetate in 5% acetonitrile) ending at 100% B (B: acetonitrile) in 4 min followed by 100% B until 5.5 min. The column oven temperature was set to $40^\circ C$. HPLC analyses were performed on an Agilent HP1100 system consisting of a G1322A Micro Vacuum Degasser, a G1311A Quaternary Pump, a G1367 Well-Plate Autosampler, a G1316A Thermostated Column Compartment and a G1315A Diode Array Detector. The diode array detector was scanned from 200 to 400 nm, step and peak width were set to 2 nm and 0.01 min, respectively. The column used was Gemini C18, 3.0×50 mm, $3.0 \mu m$, 110 \AA run at a flow rate of 1.0 mL/min. The column oven temperature was set to $40^\circ C$. A linear gradient was applied, starting at 100% A (A: 10 mM ammonium acetate in 5% acetonitrile) and ending at 95% B (B: acetonitrile) after 6.5 min then 95% B for 0.5 min. High resolution mass spectra (HRMS) were recorded on a Micromass Q-ToF micro mass spectrometer equipped with a LockSpray source and connected to an Acquity UPLC system with a PDA detector. All analyses were acquired using positive mode electrospray ionisation (ESI+) in full scan and Leucine Enkephalin (Sigma) was used as the lock mass (m/z 556.2771) at a concentration of 0.9 pmol/ μL and a flow rate of 100 μL /min with a 1:10 split, ion source:waste. Cone Voltage was set to 54 to achieve ~ 200 counts for Leucine Enkephalin. Nitrogen was used as the nebulizing and desolvation gas, with the source operated at $120^\circ C$ and the desolvation gas at $300^\circ C$. Capillary voltage was about 3000 V and cone voltage was about 30 V. Argon was used as the collision gas. Chromatographic separation for HRMS was achieved with a 2.3 min linear gradient from 95% A (A: 10 mM ammonium acetate in MilliQ water + 5% acetonitrile) to 95% B (B: acetonitrile) over an ACQUITY UPLC BEH C18 $1.7 \mu m$, 2.1×50 mm column maintained at $65^\circ C$ and run at a flow rate of 0.7 mL/min with a 1:5 split, ion source:waste. Analytes were diluted in H_2O :ACN (50:50) until suitable concentration for the LC-MS analysis.

General methods for the condensation of benzoylpyruvates (Li-1, R = H, Br) with dinucleophiles (2–5). Lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) (0.226 g, 1.00 mM) or lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = Br) (0.305 g, 1.00 mM) and the appropriate dinucleophile (2–5) (1.00 mM) were mixed together, suspended in ethanol (5.0 mL) and conc. aqueous hydrochloric acid (166 μL , 12.0M, 2.00 mM) was added. The

resulting homogeneous mixture was heated and refluxed for the times given (*vide supra*). After heating, the reaction mixture was allowed to slowly cool to ambient temperature. In case of precipitation, the deposited material was collected, washed with ethanol, and the mother liquor was evaporated *in vacuo*. Upon evaporation, the remnant was recrystallized from ethanol and further cropped.

If no initial precipitation occurred, the reaction mixture was evaporated *in vacuo*, whereupon the remnant was dissolved in chloroform and washed with dilute aqueous sodium hydroxide. The organic phase was subsequently evaporated *in vacuo* and the remnant was dissolved in hot methanol, ethanol, or extracted with boiling hexane. Subsequently, upon cooling crystallization ensued and the deposited material was cropped.

Ethyl 4-(4-bromophenyl)-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (6a). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = Br) and 3-aminopyrazole (2a). Yield: 0.259 g (75%). 1H NMR ($CDCl_3$): δ 1.49 (t, 3H, $J = 7.2$ Hz), 4.56 (q, 2H, $J = 7.1$ Hz), 7.05 (d, 1H, $J = 2.3$ Hz), 7.70 (s, 1H), 7.7–7.8 (m, 2H), 8.0–8.1 (m, 2H), 8.28 (d, 1H, $J = 2.3$ Hz). ^{13}C NMR ($CDCl_3$): δ 14.3, 62.8, 100.0, 106.7, 126.1, 129.4, 130.8, 132.0, 145.98, 146.01, 146.3, 148.9, 164.0. HRMS: Found 346.0198, Calcd. for $C_{15}H_{13}BrN_3O_2$: 346.0191.

Ethyl 4-phenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (6b). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 3-aminopyrazole (2a). Yield: 0.185 g (69%). 1H NMR ($CDCl_3$): δ 1.50 (t, 3H, $J = 7.1$ Hz), 4.57 (q, 2H, $J = 7.1$ Hz), 7.05 (d, 1H, $J = 2.5$ Hz), 7.6–7.7 (m, 3H), 7.71 (s, 1H), 8.1–8.2 (m, 2H), 8.29 (d, 1H, $J = 2.3$ Hz). ^{13}C NMR ($CDCl_3$): δ 14.3, 62.7, 99.8, 106.9, 128.8, 129.3, 130.6, 131.4, 146.0, 146.4, 147.2, 149.0, 164.1. HRMS: Found 268.1097, Calcd. for $C_{15}H_{14}N_3O_2$: 268.1086.

Ethyl 7-(4-bromophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-5-carboxylate (6d). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = Br) and 3-amino-1,2,4-triazole (2c). Yield: 0.255 g (73%). 1H NMR ($CDCl_3$): δ 1.50 (t, 3H, $J = 7.2$ Hz), 4.57 (q, 2H, $J = 7.1$ Hz), 7.78 (d, 2H, $J = 8.6$ Hz), 8.03 (s, 1H), 8.11 (d, 2H, $J = 8.60$ Hz), 8.70 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2, 63.2, 108.6, 127.4, 128.0, 130.9, 132.4, 147.8, 151.9, 155.7, 157.6, 163.5. HRMS: Found 347.0151, Calcd. for $C_{14}H_{12}BrN_4O_2$: 347.0144.

Ethyl 7-phenyl-[1,2,4]triazolo[1,5-a]pyrimidine-5-carboxylate (6e). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 3-amino-1,2,4-triazole (2c). Yield: 0.187 g (70%). 1H NMR ($CDCl_3$): δ 1.40 (t, 3H, $J = 7.1$ Hz), 4.57 (q, 2H, $J = 7.1$ Hz), 7.6–7.7 (m, 3H), 8.04 (s, 1H), 8.1–8.2 (m, 2H), 8.70 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2, 63.1, 108.8, 129.1, 129.3, 129.5, 132.4, 149.0, 151.8, 155.7, 157.6, 163.5. HRMS: Found 269.1039, Calcd. for $C_{14}H_{13}N_4O_2$: 269.1039.

Ethyl 2-azido-6-(4-bromophenyl)pyrimidine-4-carboxylate (12f). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = Br) and 5-aminotetrazole (2d). Yield: 0.277 g (79%). 1H NMR ($CDCl_3$): δ 1.46 (t, 3H, $J = 7.1$ Hz), 4.51 (q, 2H, $J = 7.2$ Hz), 7.6–7.7 (m, 2H), 8.0–8.1 (m, 2H), 8.11 (s, 1H). ^{13}C

NMR (CDCl₃): δ 14.2, 62.9, 111.9, 127.2, 128.9, 132.4, 133.9, 158.2, 163.0, 163.7, 167.0. HRMS: Found 348.0099, Calcd. for C₁₃H₁₁BrN₅O₂: 348.0096.

Ethyl 2-azido-6-phenyl-pyrimidine-4-carboxylate (12g). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 5-aminotetrazole (2d). Yield: 0.182 g (68%). ¹H NMR (CDCl₃): δ 1.47 (t, 3H, *J* = 7.1 Hz), 4.51 (q, 2H, *J* = 7.1 Hz), 7.5–7.6 (m, 3H), 8.15 (s, 1H), 8.2 (m, 2H). ¹³C NMR (CDCl₃): δ 14.1, 62.8, 112.2, 127.5, 129.1, 132.2, 134.5, 157.9, 162.9, 163.8, 168.2. HRMS: Found 270.0993, Calcd. for C₁₃H₁₂N₅O₂: 270.0991.

Ethyl 4-(4-bromophenyl)pyrimido[1,2-*b*]indazole-2-carboxylate (6h). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = Br) and 3-aminoindazole (2e). Yield: 0.339 g (85%). ¹H NMR (CDCl₃): δ 1.54 (t, 3H, *J* = 7.1 Hz), 4.60 (q, 2H, *J* = 7.2 Hz), 7.4–7.5 (m, 1H), 7.7–7.8 (m, 1H), 7.8–7.9 (m, 2H), 7.9–8.0 (m, 1H), 8.09 (s, 1H), 8.1–8.2 (m, 2H), 8.5–8.6 (m, 1H). ¹³C NMR (CDCl₃): δ 14.4, 62.7, 110.9, 114.7, 117.0, 121.6, 122.4, 126.0, 129.7, 130.6, 131.0, 132.2, 141.7, 143.5, 144.4, 151.7, 164.1. HRMS: Found 396.0349, Calcd. for C₁₉H₁₅BrN₃O₂: 396.0348.

Ethyl 4-phenylpyrimido[1,2-*b*]indazole-2-carboxylate (6i). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 3-aminoindazole (2e). Yield: 0.277 g (87%). ¹H NMR (CDCl₃): δ 1.54 (t, 3H, *J* = 7.1 Hz), 4.60 (q, 2H, *J* = 7.1 Hz), 7.4–7.5 (m, 1H), 7.6–7.8 (m, 4H), 7.9–8.0 (m, 1H), 8.11 (s, 1H), 8.2–8.3 (m, 2H), 8.4–8.6 (m, 1H). ¹³C NMR (CDCl₃): δ 14.4, 62.6, 111.2, 114.7, 117.0, 121.6, 122.2, 128.9, 129.5, 130.4, 131.0, 131.4, 141.8, 144.4, 144.7, 151.8, 164.2. HRMS: Found 318.1250, Calcd. for C₁₉H₁₆N₃O₂: 318.1243.

Ethyl 4-(4-bromophenyl)pyrrolo[2,1-*f*]pyridazine-2-carboxylate (7a). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = Br) and 1-aminopyrrole (3a). Yield: 0.292 g (85%). ¹H NMR (CDCl₃): δ 1.48 (t, 3H, *J* = 7.1 Hz), 4.54 (q, 2H, *J* = 7.1 Hz), 6.72 (dd, 1H, *J* = 4.3 Hz, 1.5 Hz), 7.06 (dd, 1H, *J* = 4.4 Hz, 2.9 Hz), 7.28 (s, 1H) 7.6–7.8 (m, 4H), 8.02 (dd, 1H, *J* = 2.8 Hz, 1.5 Hz). ¹³C NMR (CDCl₃): δ 14.3, 62.3, 100.5, 108.0, 115.7, 119.1, 124.0, 125.4, 129.6, 132.1, 135.0, 139.6, 142.2, 163.9. HRMS: Found 345.0248, Calcd. for C₁₆H₁₄BrN₂O₂: 345.0239.

Ethyl 4-phenylpyrrolo[2,1-*f*]pyridazine-2-carboxylate (7b). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = H) and 1-aminopyrrole (3a). Yield: 0.211 g (79%). ¹H NMR (CDCl₃): δ 1.48 (t, 3H, *J* = 7.2 Hz), 4.54 (q, 2H, *J* = 7.1 Hz), 6.77 (dd, 1H, *J* = 4.4 Hz, 1.4 Hz), 7.05 (dd, 1H, *J* = 4.3 Hz, 2.8 Hz), 7.32 (s, 1H), 7.5–7.6 (m, 3H), 7.7–7.8 (m, 2H), 8.02 (dd, 1H, *J* = 2.8 Hz, 1.3 Hz). ¹³C NMR (CDCl₃): δ 14.3, 62.3, 100.6, 108.1, 115.6, 118.9, 125.8, 128.1, 128.9, 129.7, 136.1, 140.9, 142.2, 164.1. HRMS: Found 267.1133, Calcd. for C₁₆H₁₅N₂O₂: 267.1134.

Ethyl 8-(4-bromophenyl)-[1,2,4]triazolo[3,4-*f*]pyridazine-6-carboxylate (7c). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = Br) and *N*-4-amino-1,2,4-triazole (3b). Yield: 0.248 g (71%). ¹H NMR (CDCl₃): δ 1.52 (t, 3H, *J* = 7.1 Hz), 4.59 (q, 2H, *J* = 7.2 Hz), 7.7–7.8 (m, 2H), 8.03 (s,

1H), 8.3–8.4 (m, 2H), 9.33 (s, 1H). ¹³C NMR (CDCl₃): δ 14.2, 63.5, 115.3, 126.8, 130.1, 130.7, 132.5, 136.5, 139.9, 142.9, 146.3, 162.2. HRMS: Found 347.0151, Calcd. for C₁₄H₁₂BrN₄O₂: 347.0144.

Ethyl 8-phenyl-[1,2,4]triazolo[3,4-*f*]pyridazine-6-carboxylate (7d). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 4-amino-1,2,4-triazole (3b). Yield: 0.174 g (65%). ¹H NMR (CDCl₃): δ 1.51 (t, 3H, *J* = 7.1 Hz), 4.58 (q, 2H, *J* = 7.2 Hz), 7.5–7.6 (m, 3H), 8.03 (s, 1H), 8.3–8.4 (m, 2H), 9.33 (s, 1H). ¹³C NMR (CDCl₃): δ 14.2, 63.4, 115.5, 129.2, 129.3, 131.4, 131.8, 137.8, 139.8, 143.2, 146.3, 162.3. HRMS: Found 269.1043, Calcd. for C₁₄H₁₃N₄O₂: 269.1039.

Ethyl 6-(4-bromophenyl)-1-methyl-pyrazolo[3,4-*b*]pyridine-4-carboxylate (8a). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = Br) and 3-amino-2-methyl-2H-pyrazole (4a). Yield: 0.253 g (70%). ¹H NMR (CDCl₃): δ 1.53 (t, 3H, *J* = 7.1 Hz), 4.25 (s, 3H), 4.56 (q, 2H, *J* = 7.1 Hz), 7.6–7.7 (m, 2H), 8.0–8.1 (m, 2H), 8.21 (s, 1H), 8.39 (s, 1H). ¹³C NMR (CDCl₃): δ 14.3, 34.0, 62.0, 111.9, 114.6, 124.3, 128.9, 131.89, 131.93, 132.5, 137.2, 151.5, 155.3, 165.1. HRMS: Found 360.0342, Calcd. for C₁₆H₁₅BrN₃O₂: 360.0348.

Ethyl 1-methyl-6-phenyl-pyrazolo[3,4-*b*]pyridine-4-carboxylate (8b). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 3-amino-2-methyl-2H-pyrazole (4a). Yield: 0.196 g (70%). ¹H NMR (CDCl₃): δ 1.52 (t, 3H, *J* = 7.1 Hz), 4.25 (s, 3H), 4.54 (q, 2H, *J* = 7.1 Hz), 7.5–7.6 (m, 3H), 8.2 (m, 2H), 8.23 (s, 1H), 8.38 (s, 1H). ¹³C NMR (CDCl₃): δ 14.3, 34.1, 61.9, 111.7, 115.2, 127.5, 128.9, 129.7, 128.9, 131.8, 132.5, 138.5, 151.7, 156.7, 165.3. HRMS: Found 282.1249, Calcd. for C₁₆H₁₆N₃O₂: 282.1243.

Ethyl 4-(4-bromophenyl)-5,7-dimethoxy-quinoline-2-carboxylate (9b). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = H) and 3,5-dimethoxyaniline (5b). Yield: 0.342 g (82%). ¹H NMR (CDCl₃): δ 1.46 (t, 3H, *J* = 7.1 Hz), 3.53 (s, 3H), 3.96 (s, 3H), 4.53 (q, 2H, *J* = 7.1 Hz), 6.55 (d, 1H, *J* = 2.3 Hz), 7.1–7.2 (m, 2H), 7.38 (d, 1H, *J* = 2.3 Hz), 7.5–7.6 (m, 2H), 7.76 (s, 1H). ¹³C NMR (CDCl₃): δ 14.3, 55.3, 55.8, 62.3, 101.2, 101.3, 115.7, 121.0, 121.3, 129.8, 130.2, 140.8, 147.2, 148.2, 150.9, 156.6, 161.6, 165.0. HRMS: Found 416.0509, Calcd. for C₂₀H₁₉BrNO₄: 416.0497.

Ethyl 5,7-dimethoxy-4-phenyl-quinoline-2-carboxylate (9c). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 3,5-dimethoxyaniline (5b). Yield: 0.248 g (73%). ¹H NMR (CDCl₃): δ 1.47 (t, 3H, *J* = 7.2 Hz), 3.51 (s, 3H), 3.97 (s, 3H), 4.54 (q, 2H, *J* = 7.1 Hz), 6.55 (d, 1H, *J* = 2.3 Hz), 7.3 (m, 2H), 7.35 (d, 1H, *J* = 2.0 Hz), 7.4 (m, 3H), 7.83 (s, 1H). ¹³C NMR (CDCl₃): δ 14.4, 55.3, 55.8, 62.2, 101.1, 101.5, 116.0, 121.3, 127.0, 127.1, 128.1, 142.0, 147.4, 149.3, 151.1, 156.9, 161.3, 165.3. HRMS: Found 338.1389, Calcd. for C₂₀H₂₀NO₄: 338.1392.

Ethyl 4-(4-bromophenyl)-7-(dimethylamino)quinoline-2-carboxylate (9d). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = H) and 3-(*N,N*-dimethylamino)aniline (5c). Yield: 0.360 g (90%). ¹H NMR (CDCl₃): δ 1.48 (t, 3H, *J* = 7.1 Hz), 3.13 (s, 6H), 4.54 (q, 2H, *J* = 7.1 Hz), 7.21 (dd,

1H, $J = 9.4$ Hz, 2.8 Hz), 7.4 (m, 2H), 7.42 (br. s, 1H), 7.6 (m, 2H), 7.72 (d, 1H, $J = 9.4$ Hz), 7.80 (s, 1H). ^{13}C NMR (CDCl_3): δ 14.4, 40.4, 62.1, 108.0, 117.3, 118.4, 119.8, 122.8, 125.8, 131.1, 131.7, 137.0, 147.8, 150.0, 151.3, 165.7. HRMS: Found 399.0711, Calcd. for $\text{C}_{20}\text{H}_{20}\text{BrN}_2\text{O}_2$: 399.0708.

Ethyl 7-(dimethylamino)-4-phenylquinoline-2-carboxylate (9e). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 3-(*N,N*-dimethylamino)aniline (5c). Yield: 0.231 g (72%). ^1H NMR (CDCl_3): δ 1.49 (t, 3H, $J = 7.1$ Hz), 3.13 (s, 6H), 4.56 (q, 2H, $J = 7.2$ Hz), 7.21 (dd, 1H, $J = 9.5$ Hz, 2.7 Hz), 7.45 (br. s, 1H), 7.5–7.6 (m, 5H), 7.80 (d, 1H, $J = 9.4$ Hz), 7.85 (s, 1H). ^{13}C NMR (CDCl_3): δ 14.4, 40.4, 62.1, 107.8, 117.6, 118.3, 120.3, 126.3, 128.46, 128.53, 129.5, 138.1, 147.6, 149.3, 149.9, 151.3, 165.7. HRMS: Found 321.1612, Calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2$: 321.1603.

Ethyl 4-(4-bromophenyl)-7H-pyrrolo[2,3-*h*]quinoline-2-carboxylate (9f). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-(4'-bromophenyl)butyric acid ethyl ester (Li-1, R = H) and 4-amino-1H-indole (5d). Yield (based on prep. HPLC of 0.080 g crude material): 0.020 g (25%). ^1H NMR ($\text{DMSO}-d_6$): δ 1.21 (t, 3H, $J = 7.1$ Hz), 4.11 (q, 2H, $J = 7.2$ Hz), 5.08 (s, 1H), 6.2–6.3 (m, 1H), 6.3–6.4 (m, 1H), 6.6–6.7 (m, 2H), 7.3–7.5 (m, 2H), 7.5–7.7 (m, 2H) 8.31 (s, 1H), 11.02 (d, 1H, $J = 2.0$ Hz). ^{13}C NMR ($\text{DMSO}-d_6$): δ 14.0, 61.3, 79.2, 113.2, 116.7, 117.5, 120.6, 122.1, 124.0, 125.2, 127.3, 128.1, 131.8, 138.5, 139.6, 144.5, 152.0, 156.0, 165.3. HRMS: Found 395.0403, Calcd. for $\text{C}_{20}\text{H}_{16}\text{BrN}_2\text{O}_2$: 395.0395.

Ethyl 4-phenyl-7H-pyrrolo[2,3-*h*]quinoline-2-carboxylate (9g). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 4-amino-1H-indole (5d). Yield (based on prep. HPLC of 0.080 g crude material): 0.018 g (23%). ^1H NMR (CDCl_3): δ 1.30 (t, 3H, $J = 7.2$ Hz), 4.23 (q, 2H, $J = 7.2$ Hz), 5.45 (s, 1H), 6.25 (s, 1H), 6.48 (d, 1H, $J = 6.8$ Hz), 6.6–6.8 (m, 2H), 7.3–7.5 (m, 5H), (br. s, 1H). ^{13}C NMR (CDCl_3): δ 14.0, 62.1, 112.6, 117.9, 119.9, 121.7, 121.8, 125.6, 126.1, 127.7, 128.6, 129.1, 139.3, 139.9, 144.8, 153.3, 156.3, 165.9. HRMS: Found 317.1282, Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2$: 317.1290.

Ethyl 5-phenyl-1H-pyrrolo[3,2-*g*]quinoline-7-carboxylate (9i). The title compound was obtained by the reaction of lithio 2,4-dioxo-4-phenylbutyric acid ethyl ester (Li-1, R = H) and 6-amino-1H-indole (5e). Yield (based on prep. HPLC of 0.080 g crude material): 0.022 g (28%). ^1H NMR (CDCl_3): δ 1.50 (t, 3H, $J = 7.2$ Hz), 4.57 (q, 2H, $J = 7.2$ Hz), 6.67 (dd, 1H, $J = 3.0$ Hz, 2.3 Hz), 7.08 (t, 1H, $J = 2.9$ Hz), 7.5–7.6 (m, 2H), 7.6–7.7 (m, 3H), 7.91 (br. s, 1H), 8.0–8.1 (m, 2H), 8.10 (s, 1H). ^{13}C NMR (CDCl_3): δ 14.2, 62.1, 104.0, 117.0, 121.7, 123.7, 124.3, 125.4, 126.4, 128.5, 128.6, 129.3, 129.5, 139.8, 141.4, 144.4, 144.8, 146.5, 165.7. HRMS: Found 317.1299, Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2$: 317.1290.

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- [16] Calculations were performed using the Jaguar program (v7.5) from Schrodinger Inc using the B3LYP functional and the LACVP** basis set. The relative energies includes solvent effects using the PBF approximation.
- [17] For structure **15b**, the C-O bond of the carbonyl proximal to the ester moiety is more elongated compared to the benzylic carbonyl (1.33Å vs. 1.31Å) and therefore more electrophilic. This is in line with the observed regiochemical preference in this reaction.
- [18] Crystallographic details are available in the supporting information.