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

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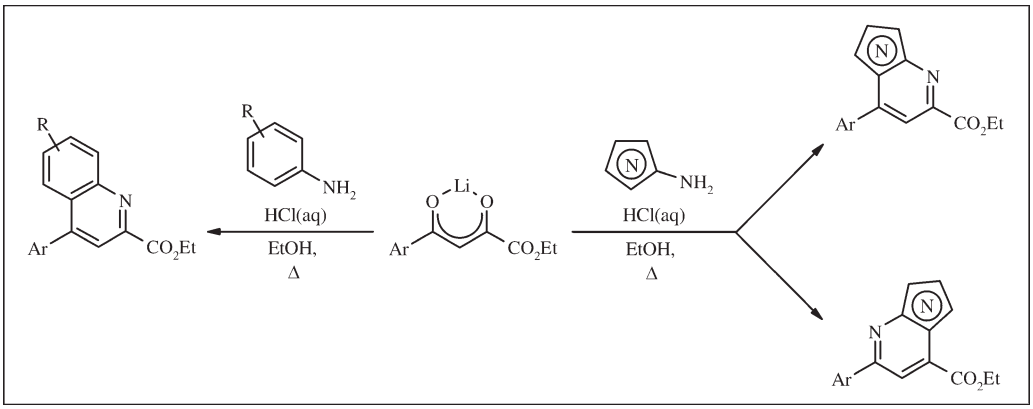

Acid-mediated condensation between benzoylpyruvates and various dinucleophiles in alcoholic solvent furnished the heterocyclic imprint in moderate to good yield. Combining a range of symmetric as well as nonsymmetric nitrogen/nitrogen or nitrogen/carbon centered dinucleophiles resulted in excellent regioselectivity. 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].

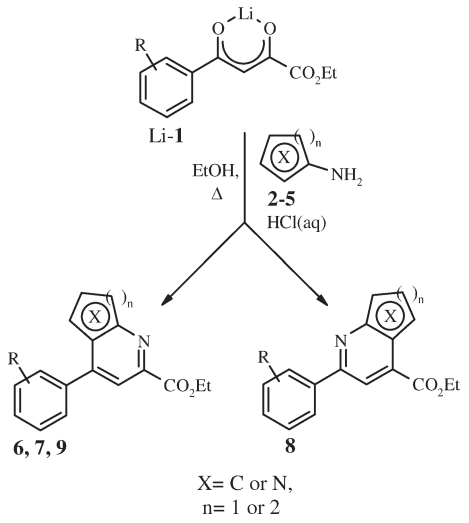
Herein, we want to report a convenient route for the preparation of novel γ-arylated aza-heterocyclic esters by highly chemo- and regioselective condensation of lithio benzoylpyruvate **1** with aromatic amines **2–5** (Scheme 1). Considering the number of different benzoylpyruvates **1** readily available from commercial acetophenones **10**, this protocol can be seen as an alternative to arylation of the parent heterocyle 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

Scheme 1



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-stabile 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.

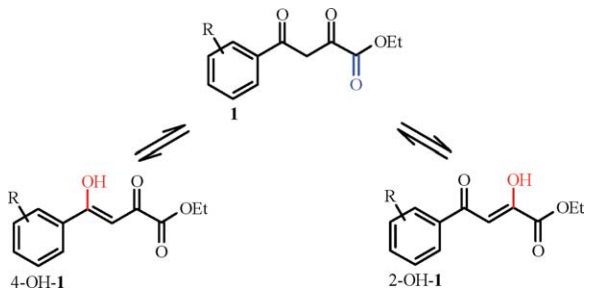
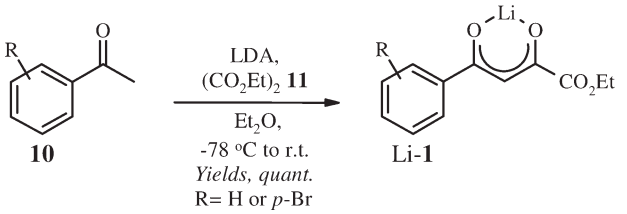


Figure 1. Tautomery in benzoylpyruvates. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 2



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 tautomery [15]. At the outset, it was expected that the initially formed tetrazolo[1,5-*a*]pyrimidines **6f** and **6g** could undergo

Scheme 3

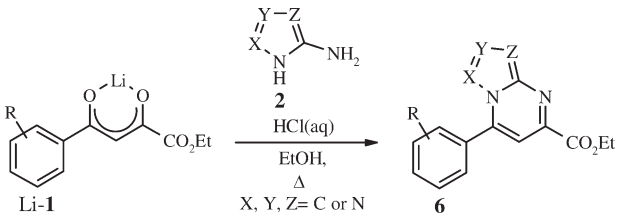


Table 1

Synthesis of [*a*]-fused pyrimidines **6**.[a]

Entry	Product	R	Aryl amine	Time (h)[c]	Yield (%)[d]
1	**6a**	*p*-Br	1H-Pyrazol-5-yl **2a**	13	75
2	**6b**	H	1H-Pyrazol-5-yl **2a**	13	69
3	**6c**	*p*-Br	1H-Imidazol-5-yl **2b**	96[e]	n.r.
4	**6d**	*p*-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]	*p*-Br	1H-Tetrazol-5-yl **2d**	13	79
7	**6g**[b]	H	1H-Tetrazol-5-yl **2d**	13	68
8	**6h**	*p*-Br	2H-Indazol-3-yl **2e**	13	85
9	**6i**	H	2H-Indazol-3-yl **2e**	13	87
10	**6j**	*p*-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-heterocylic 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 operational 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-dinucleo-philes **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

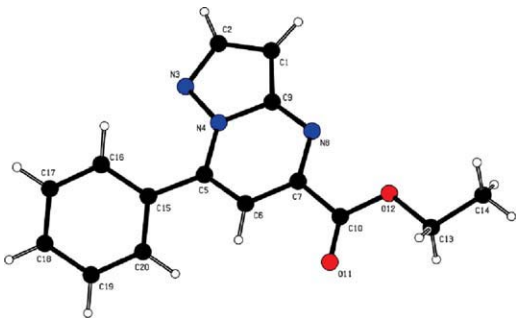


Figure 2. Crystal structure of compound **6b** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

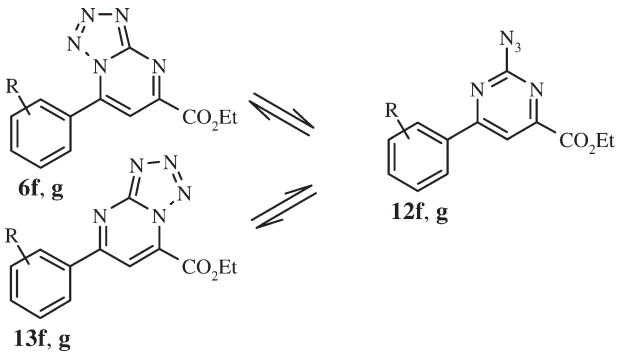


Figure 3. Valence tautomery in tetrazolo[1,5-a]pyrimidine **6f** and **6g**.

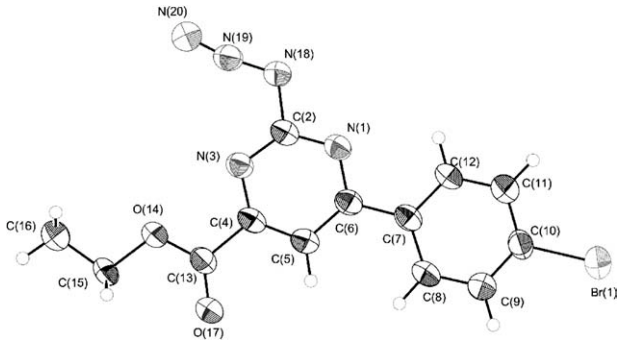


Figure 4. ORTEP presentation of compound **12f**.

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 Skraup–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

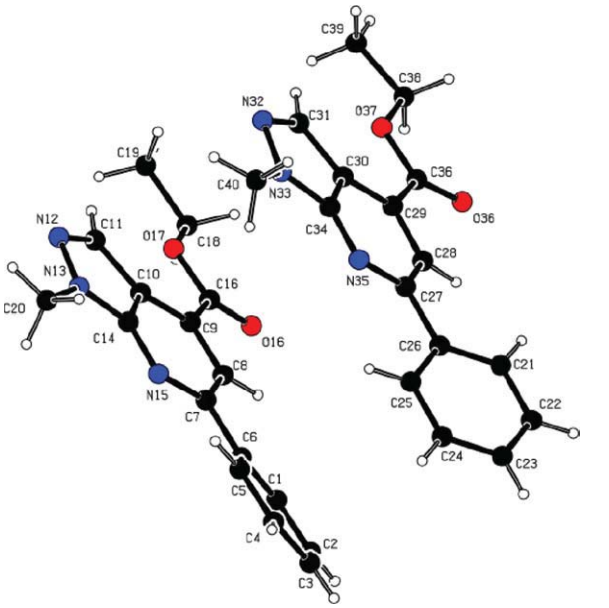
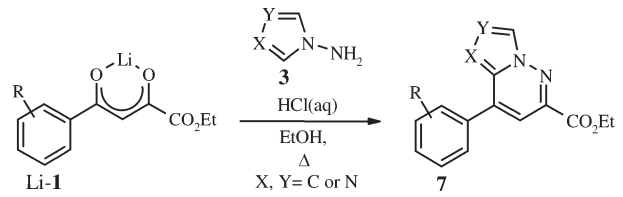


Figure 5. Crystal structure of compound **8b** determined by single-crystal diffraction technique at 200 K. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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 tautomery available to the fused rings. Thus, in the pertinent case, ^{1}H NMR indicates that the extended 14 π-electron system

Scheme 4



Scheme 5

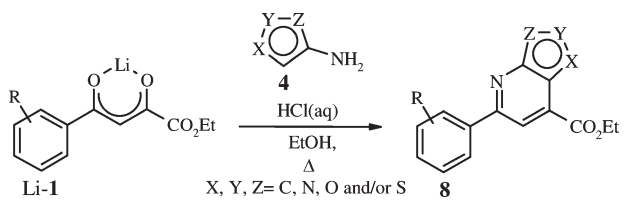


Table 2

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

Entry	Product	R	Aryl amine	Time (h)[b]	Yield (%)[c]
1	**7a**	*p*-Br	Pyrrol-1-yl **3a**	0.5	85
2	**7b**	H	Pyrrol-1-yl **3a**	0.5	79
3	**7c**	*p*-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**	*p*-Br	2-Methyl-2H-pyrazol-3-yl **4a**	120	70
2	**8b**	H	2-Methyl-2H-pyrazol-3-yl **4a**	120	70
3	**8c**	*p*-Br	5-Methylisox-azole-3-yl **4b**	120	n.r.
4	**8d**	*p*-Br	3-Methylisothi-azol-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.

Scheme 6

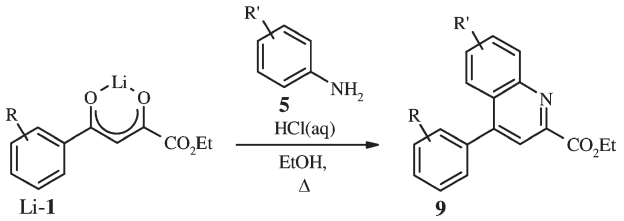


Table 4

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

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

[a] The reactions were performed with equimolar proportions of Li-1 and amine 5 in the presence of 2 equiv. of HCl (aq).
[b] Time to achieve full conversion or no further reaction occurred by HPLC or LC-MS.
[c] Isolated yield.
[d] Preparative 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 tautomery is less pronounced. However, in general the quinolines **9** were less stabile 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-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

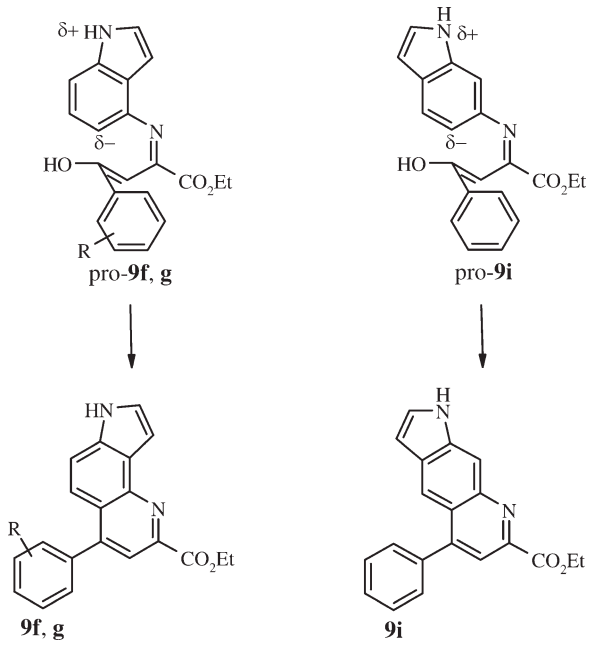


Figure 6. Tricycles resulting from condensation with 4-amino-1H-indole **5e** and 6-amino-1H-indole **5f**.

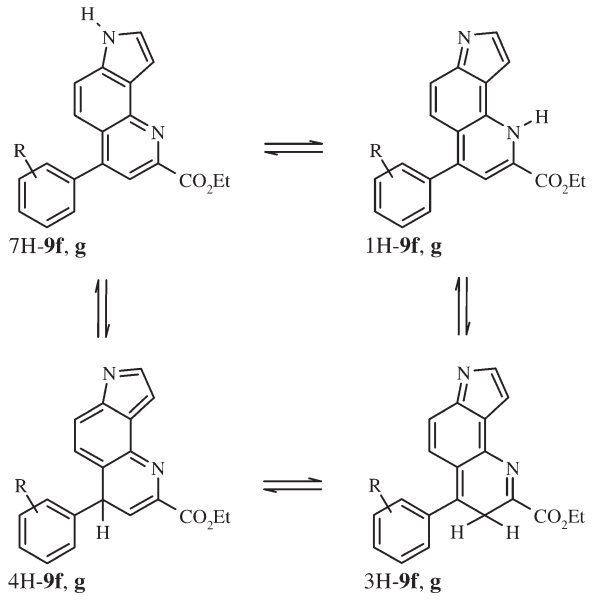
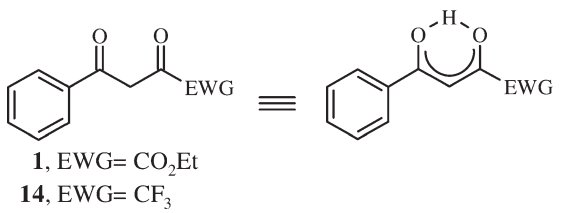


Figure 7. Tautomery in pyrrolo[2,3-h]quinolines **9f** and **9g**.

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.



1, EWG= CO_2Et
14, EWG= CF_3

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

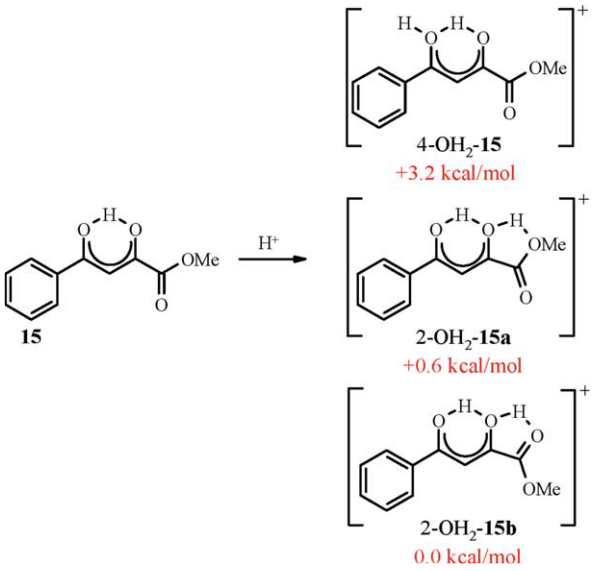


Figure 10. Calculated relative energies of protonated model benzoylpyruvate 15 based on B3LYP/6-31G**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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 Kα radiation (λ = 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 ^{1}H, and 101 MHz for ^{13}C equipped with a four-nucleus probe-head with Z-gradients, or a Bruker Avance III 500 NMR spectrometer, operating at 500 MHz for ^{1}H and 126 MHz for ^{13}C 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°C ± 2°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°C and the pressure was set to 1.9 bar. Separation was performed on Gemini C18 3.0 × 50, 3 μm (Phenomenex) run at a flow rate of 1 mL/min. A linear gradient was applied starting at 100% A (A: 10 m*M* 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°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 μm, 110 Å run at a flow rate of 1.0 mL/min. The column oven temperature was set to 40°C. A linear gradient was applied, starting at 100% A (A: 10 m*M* 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°C and the desolvation gas at 300°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 m*M* ammonium acetate in MilliQ water + 5% acetonitrile) to 95% B (B: acetonitrile) over an ACQUITY UPLC BEH C18 1.7 μm, 2.1 × 50 mm column maintained at 65°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 m*M*) or lithio 2,4-dioxo-4-(4′-bromophenyl)butyric acid ethyl ester (Li-**1**, R = Br) (0.305 g, 1.00 m*M*) and the appropriate dinucleophile (**2–5**) (1.00 m*M*) were mixed together, suspended in ethanol (5.0 mL) and conc. aqueous hydrochloric acid (166 μL, 12.0*M*, 2.00 m*M*) 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%). ^{1}H 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%). ^{1}H 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%). ^{1}H 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%). ^{1}H 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%). ^{1}H 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 ($CDCl_3$): 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 $C_{13}H_{11}BrN_5O_2$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{13}H_{12}N_5O_2$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{19}H_{15}BrN_3O_2$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{19}H_{16}N_3O_2$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{16}H_{14}BrN_2O_2$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{16}H_{15}N_2O_2$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{14}H_{12}BrN_4O_2$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{14}H_{13}N_4O_2$: 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-2*H*-pyrazole (**4a**). Yield: 0.253 g (70%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{16}H_{15}BrN_3O_2$: 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-2*H*-pyrazole (**4a**). Yield: 0.196 g (70%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{16}H_{16}N_3O_2$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{20}H_{19}BrNO_4$: 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%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): 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 $C_{20}H_{20}NO_4$: 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%). ^{1}H NMR ($CDCl_3$): 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 $C_{20}H_{20}BrN_2O_2$: 399.0708.

Ethyl 7-(dimethylamino)-4-phenyl-quinoline-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%). ^{1}H 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 $C_{20}H_{21}N_2O_2$: 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-1*H*-indole (**5d**). Yield (based on prep. HPLC of 0.080 g crude material): 0.020 g (25%). ^{1}H NMR (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 (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 $C_{20}H_{16}BrN_2O_2$: 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-1*H*-indole (**5d**). Yield (based on prep. HPLC of 0.080 g crude material): 0.018 g (23%). ^{1}H 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 $C_{20}H_{17}N_2O_2$: 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-1*H*-indole (**5e**). Yield (based on prep. HPLC of 0.080 g crude material): 0.022 g (28%). ^{1}H 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 $C_{20}H_{17}N_2O_2$: 317.1290.

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REFERENCES AND NOTES

[1] Astles, P. C.; Harper, M. F.; Harris, N. V.; McLay, I.M.; Walsh, R. J. A.; Lewis, R. A.; Smith, C.; Porter, B.; McCarthy, C. PCT Int Appl 1995, WO 95/13262 A1, 191.

[2] Barth, F.; Casellas, P.; Congy, C.; Martinez, S.; Rinaldi, M.; Anne-Archard, G. U.S. Pat. Appl 1997, US 5624941 A, 45.

[3] Ghosh, S.; Elder, A. M.; Carson, K. G.; Sprott, K.; Harrison, S. PCT Int Appl 2004, WO 2004/032848 A2, 257.

[4] Goodfellow, V.; Rowbottom, M.; Dyck, B. P.; Tamiya, J.; Zhang, M.; Grey, J.; Vickers, T.; Kiankarimi, M.; Wade, W.; Hudson, S.C. PCT Int Appl 2004, WO 2004/080411 A2, 86.

[5] Makings, L.R.; Grootenhuis, P.; Hurley, D.J.; Tung, R.D.; Termin, A.P. PCT Int Appl 2004, WO 2004/108133 A2, 79.

[6] Lee, J.; Kim, H. J.; Choi, S.; Choi, H. G.; Yoon, S.; Kim, J.-H.; Jo, K.; Kim, S.; Koo, S.-Y.; Kim, M.-H.; Kim, J. I.; Hong, S.-Y.; Kim, M. S.; Ahn, S.; Yoon, H.-S.; Cho, H.-S. PCT Int Appl 2004, WO 2004/080979 A1, 106.

[7] Anderson, D. R.; Stehle, N. W.; Kolodziej, S. A.; Reinhard, E. J. PCT Int Appl 2004, WO 2004/055015 A1, 223.

[8] Nolsöe, J. M. J.; Weigelt, D. J Heterocyclic Chem 2009, 46, 1.

[9] Freri, M. Gazz Chim Ital 1938, 68, 612.

[10] Butenandt, A.; Hallmann, G.; Beckmann, R. Chem Ber 1957, 90, 1120.

[11] Murray, W. V.; Wachter, M. P. J. Heterocyclic Chem 1989, 26, 1389.

[12] Grimmett, M. R. In Comprehensive Organic Chemistry; Barton, D. H. R., Ollis, W. D., Sammes, P. G., Eds.; Pergamon: New York, 1979; Vol. 4, p 357.

[13] Sokololova, M. M.; Ostrovskii, V. A.; Koldobskii, G. I.; Mel'nikov, V. V.; Gidaspov, B. V. Zh Org Khim 1974, 10, 1085.

[14] Filyakova, V. I.; Kuznetsova, O. A.; Ulomskii, E. N.; Rybalova, T. V.; Gatilov, Yu. V.; Kodess, M. I.; Rusinov, V. L.; Pashkevich, K. I. Russ Chem Bull Int Ed 2002, 51, 332.

[15] Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D.; Chen, Y.-J. J Org Chem 2006, 71, 6592 and references therein.

[16] Calculations where 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.