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Regio- and Diastereoselective Synthesis of Novel Polycyclic Pyrrolo[2,1-*a*]isoquinolines Bearing Indeno[1,2-*b*]quinoxaline Moieties by a Three-Component [3+2]-Cycloaddition Reaction

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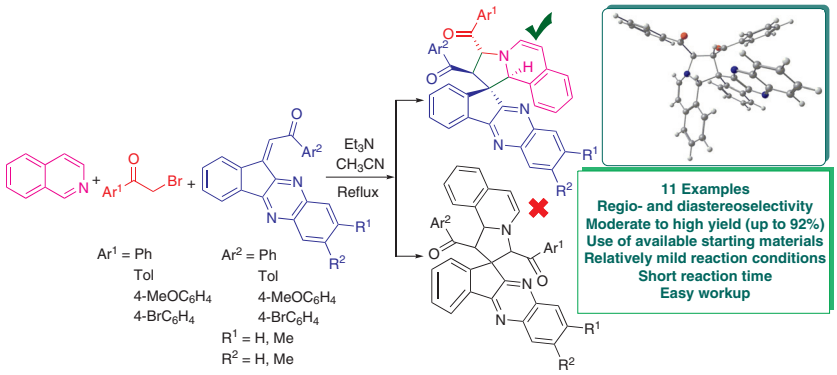

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Abstract A regio- and diastereoselective synthesis of 2,3-dihydro-10b′*H*-spiro[indeno[1,2-*b*]quinoxaline-11,1′-pyrrolo[2,1-*a*]isoquinoline]-2′,3′-diylbis(phenylmethanone) derivatives containing four contiguous chiral stereocenters was achieved through 1,3-dipolar cycloaddition of isoquinolinium *N*-ylides in a one-pot three-component reaction. The desired products were obtained in short reaction times and in moderate to high yields (up to 92%) under relatively mild reaction conditions. The structure and relative stereochemistry of the desired product was confirmed by X-ray diffraction analysis.

Key words pyrroloisoquinolines, indenoquinoxalines, spiro compounds, diastereoselectivity, 1,3-dipolar cycloaddition, multicomponent reaction

Pyrrolo[2,1-*a*]isoquinolines, which have a broad range of applications, are attractive target structures in synthesis and in medicinal chemistry.[1a] Furthermore, these heterocycles are important frameworks in such natural products as (+)-oleracein,[1b] (–)-trolline,[1c] (+)-crispine,[1d] and lamellarin alkaloids, for example, lamellarin D and lamellarin α-20-sulfate[1e] (Figure 1).[1f] Most alkaloids containing pyrrolo[2,1-*a*]isoquinoline residues exhibit significant antitumor,[2] antibacterial, antiviral,[1c,3] antiinflammatory,[4] antidepressant,[5] or cardiovascular activities.[6]

Quinoxaline and its derivatives are also important heterocycles that have a wide range of biological activities, such as antimicrobial,[7] antihypertensive,[8] antitubercular,[9] antidepressant,[10] antimalarial,[11] antiinflammatory,[12] anticonvulsant,[13] anti-HIV,[14] antidiabetic, or anticancer activities[15,16] (Figure 2). In addition, they have been used in syntheses of organic semiconductors,[17] as rigid subunits of macrocyclic receptors for molecular recognition,[18] and as chemically controllable switches.[19] Indenoquinoxalines are a major group of polycyclic quinoxalines that are widely used as precursors for the synthesis of biologically active spiro compounds.[20]

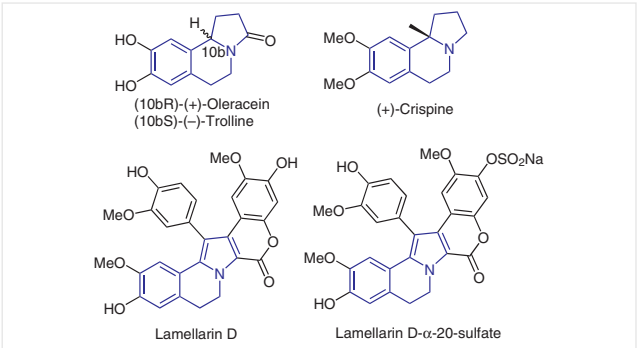

Figure 1 Examples of pyrrolo[2,1-*a*]isoquinoline-containing alkaloids

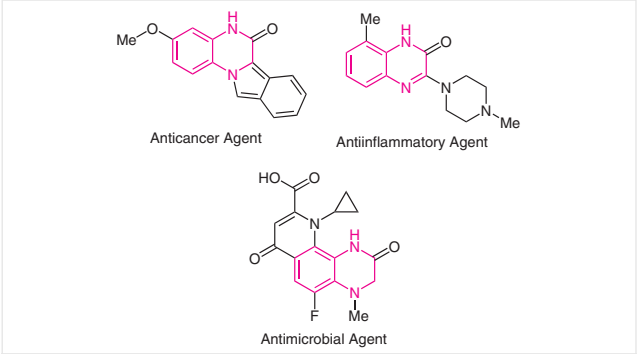

Figure 2 Examples of biologically active quinoxalines

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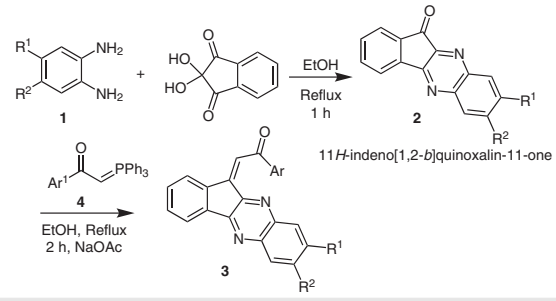
Heteroaromatic N-ylides such as pyridinium, thiazolium, quinolinium, or isoquinolinium methylides are useful reactive intermediates that are extensively used in 1,3-dipolar cycloaddition reactions for syntheses of N-bridgehead heterocyclic compounds.[21–23] The reaction of isoquinolinium N-ylides with various activated alkynes or olefins constitutes an efficient method for the regio- and stereoselective synthesis of structurally complex pyrrolo[2,1-*a*]isoquinolines with multiple contiguous stereogenic centers that have many applications in medicinal chemistry and drug discovery.[24,25] For example, Yan and co-workers reported the synthesis of spiro[indoline-3,3′-pyrrolo[1,2-*a*]isoquinolines] by a 1,3-dipolar cycloaddition reaction of *N*-phenacylquinolinium bromides with 3-phenacylideneoxindoles as dipolarophiles.[24]

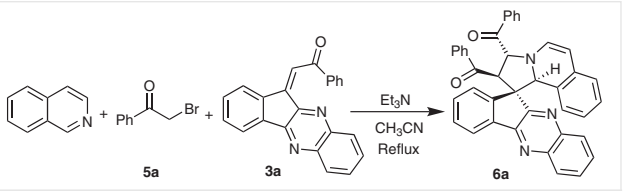
Because of the biological importance of pyrrolo[2,1-*a*]isoquinolines and quinoxaline structures, and in continuation of related studies and our growing interest in developing 1,3-dipolar cycloaddition reactions,[26–28] we decided to synthesize spiroheterocycles containing both pyrrolo[2,1-*a*]isoquinoline and quinoxaline moieties. To the best of our knowledge, this is the first report of a 1,3-dipolar cycloaddition of *N*-phenacylquinolinium bromides with 1-aryl-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanones in which electron-deficient alkenes act as dipolarophiles to give functionalized spiropyrrolo[2,1-*a*]isoquinoline derivatives bearing four stereogenic centers.

The reaction of o-phenylenediamines **1** with ninhydrin in refluxing EtOH gave the corresponding 11*H*-indeno[1,2-*b*]quinoxalin-11-ones **2** in high yields.[29] We then synthesized 1-aryl-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)-ethanones **3** through the reaction of **2** with 1-aryl-2-(triphenylphosphoranylidene)ethanones **4** in the presence of sodium acetate in EtOH, according to a previously reported method (Scheme 1).[30,31]



Scheme 1 Synthesis of 1-aryl-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanones **3**

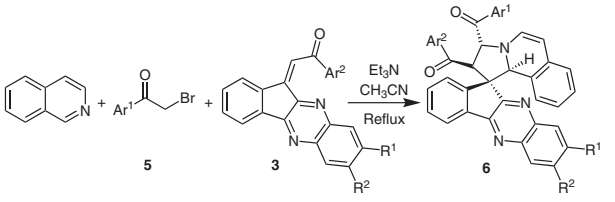
With compounds **3** in hand, we investigated the 1,3-dipolar cycloaddition of isoquinolinium N-ylides, generated in situ by the reaction of isoquinoline and phenacyl bromide (**5a**), with 2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)-1-phenylethanone (**3a**) as a dipolarophile. For this purpose, a mixture of isoquinoline and phenacyl bromide (**5a**) was stirred in acetonitrile at room temperature for 15 minutes. Ketone **3a** and triethylamine were then added, and the mixture was stirred under reflux conditions for two hours. After a simple workup, product **6a** was obtained in moderate yield (Scheme 2).



Scheme 2 Three-component synthesis of diastereoisomer **6a**

To survey the scope of this reaction, various substituted phenacyl bromides **5** containing either electron-donating or electron-withdrawing groups on the aromatic ring were treated with isoquinoline and various 1-aryl-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanones **3** under the

Table 1 Synthesis of 2′,3′-Dihydro-10b′H-spiro[indeno[1,2-*b*]quinoxaline-11,1′-pyrrolo[2,1-*a*]isoquinoline]-2′,3′-diylbis(phenylmethanone) Derivatives **6**[a]



Product	Ar^1	Ar^2	R^1	R^2	Time (h)	Yield[b] (%)
6a	Ph	Ph	H	H	2	64
6b	4-Tol	Ph	H	H	2	69
6c	4-$MeOC_6H_4$	Ph	H	H	1	76
6d	4-BrC_6H_4	Ph	H	H	0.5	90
6e	Ph	4-Tol	H	H	2	71
6f	4-Tol	4-Tol	H	H	1.5	85
6g	4-$MeOC_6H_4$	4-Tol	H	H	1	78
6h	Ph	4-$MeOC_6H_4$	H	H	1.5	75
6i	4-Tol	4-$MeOC_6H_4$	H	H	1	81
6j	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	H	0.5	87
6k	4-BrC_6H_4	4-$MeOC_6H_4$	H	H	0.5	92
6l	Ph	4-BrC_6H_4	H	H	1	73
6m	4-$MeOC_6H_4$	4-BrC_6H_4	H	H	0.5	89
6n	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	Me	2	61
6o	4-BrC_6H_4	4-$MeOC_6H_4$	Me	Me	1.5	67

[a] Reaction conditions: isoquinoline (1 mmol), **5** (1 mmol), **3** (1 mmol), Et_3N (1 mmol), CH_3CN (3 mL), reflux.
[b] Isolated yields after direct filtration of the reaction mixture.

same reaction conditions (Table 1).[32] Generally, all the products were obtained in moderate to high yields and with excellent diastereoselectivities.

The structures of the isolated products **6a–o** were fully characterized by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, and IR spectroscopy, and confirmed by single-crystal X-ray diffraction in the case of **6b** (see below). The ^{1}H NMR spectrum of **6a** contained characteristic signals with appropriate chemical shifts and coupling constant for 22 hydrogen atoms of the aromatic region. Two doublets at δ = 5.33 and 6.46 ppm with vicinal coupling constant *J* = 5.5 Hz were assigned to the protons of the dihydroisoquinoline ring. One singlet at δ = 6.36 was assigned to the benzylic CH, and two doublets at δ = 5.24 and 5.37 ppm with the vicinal coupling constant *J* = 7.5 Hz were assigned to protons of the newly formed pyrrolidine ring.

To identify the positions of the two methine protons in the pyrrolidine ring for compound **6a**, we performed density functional theory (DFT) calculations with the functional B3LYP and the 6-31+G(d) basis set. As shown in Figure 3, the dihedral angle between these two protons is 146.960°. From the ^{1}H NMR spectrum (*J* = 7.5 Hz) and considering this dihedral angle, we deduce that the two vicinal benzoyl groups in the products are in *trans*-positions.

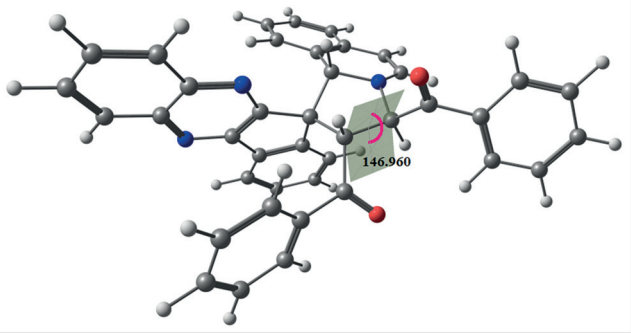


Figure 3 Optimized structure of **6a** calculated at B3LYP/6-31+G(d) level of theory. The dihedral angle in the optimized geometry is reported in degrees.

An X-ray crystallographic analysis of the related compound **6b**[33] confirmed this conclusion. As shown in Figure 4, the aryl group of the indenoquinoxaline moiety and its adjacent arylcarbonyl group exist in a *trans*-configuration. This interesting result showed that this 1,3-dipolar cycloaddition reaction proceeds with extremely high diastereoselectivity.

On the basis of the X-ray crystallography, it was clear the cycloaddition reaction between isoquinolinium N-ylides and unsymmetrical dipolarophile **3** is completely regioselective, as only one regioisomer was obtained. Our proposed mechanism for this reaction is shown in Scheme 3. First, the isoquinolinium bromide generated by the reaction of isoquinoline and phenacyl bromide (**5a**) is deprotonated by triethylamine to give the isoquinolinium ylide **A**. Compound **3a** contains one enone and one enimine unit, so a 1,3-dipolar cycloaddition reaction of dipole **A** to the exocyclic double bond of this compound might occur through one of two pathways giving regioisomers **6a** and **7a**, respectively. X-ray crystallographic analysis of product showed conclusively that the reaction proceeds by Path a to give regioisomer **6a** exclusively.

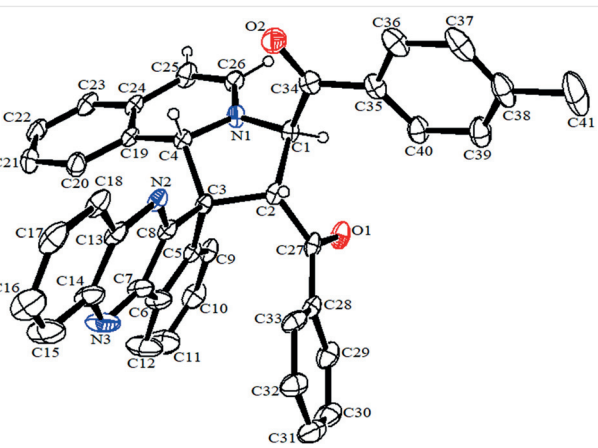
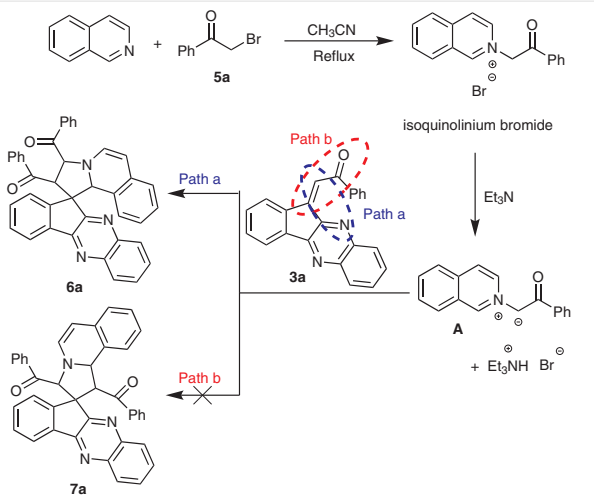


Figure 4 X-ray crystallographic structure of **6b**



Scheme 3 Proposed mechanism for the formation of the desired product **6a**

In conclusion, we have developed a simple and efficient method for the construction of spiropyrrolo[2,1-*a*]isoquinolines containing indenoquinoxaline moieties through a highly regioselective and stereoselective1,3-dipolar cycloaddition reaction of isoquinolinium ylides, generated in situ by the reaction of isoquinoline and phenacyl bromides in the presence of Et_3N, with 1-aryl-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanones. The use of readily available

starting materials, the short reaction times, the moderate to high yields, and the easy purification and high diversity of the products are among the advantages of this method.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690768. Included are experimental details, characteristic data, 1H and 13CNMR spectra of products, crystal data and the computational data of products.

References and Notes

(1) (a) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796. (b) Xiang, L.; Xing, D.; Wang, W.; Wang, R.; Ding, Y.; Du, L. *Phytochemistry* **2005**, *66*, 2595. (c) Wang, R. F.; Yang, X. W.; Ma, C. M.; Cai, S. Q.; Li, J. N.; Yukihiro, S. *Heterocycles* **2004**, *63*, 1443. (d) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795. (e) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901. (f) Andersen, R. J.; Faulkner, D. J.; Heng, H. C.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492.

(2) (a) Tangdenpaisal, K.; Worayuthakarn, R.; Karnkla, S.; Ploypradith, P.; Intachote, P.; Sengsai, S.; Saimanee, B.; Ruchirawat, S.; Chittchang, M. *Chem. Asian J.* **2015**, *10*, 925. (b) Theppawong, A.; Ploypradith, P.; Chuawong, P.; Ruchirawat, S.; Chittchang, M. *Chem. Asian J.* **2015**, *10*, 2631. (c) Plisson, F.; Huang, X. C.; Zhang, H.; Khalil, Z.; Capon, R. J. *Chem. Asian J.* **2012**, *7*, 1616.

(3) Su, B.; Cai, C.; Deng, M.; Liang, D.; Wang, L.; Wang, Q. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2881.

(4) Cavallito, C. J.; Gray, A. P. FR 2135297, **1972**; *Chem. Abstr.* **1973**, *79*, 96989

(5) Maryanoff, B. E.; Vaught, J. L.; Shank, R. P.; McComsey, D. F.; Costanzo, M. J.; Nortey, S. O. *J. Med. Chem.* **1990**, *33*, 2793.

(6) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Constanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433.

(7) Kurasawa, Y.; Kim, H. O. *J. Heterocycl. Chem.* **2002**, *39*, 551.

(8) Monge, A.; Palop, J. A.; Urbasos, I.; Fernández-Alvarez, E. *J. Heterocycl. Chem.* **1989**, *26*, 1623.

(9) Vicente, E.; Pérez-Silanes, S.; Lima, L. M.; Ancizu, S.; Burguete, A.; Solano, B.; Villar, R.; Aldana, I.; Monge, A. *Bioorg. Med. Chem.* **2009**, *17*, 385.

(10) Becker, I. *J. Heterocycl. Chem.* **2008**, *45*, 1005.

(11) Guillon, J.; Moreau, S.; Mouray, E.; Sinou, V.; Forfar, I.; Fabre, S. B.; Desplat, V.; Millet, P.; Parzy, D.; Jarry, C.; Grellier, P. *Bioorg. Med. Chem.* **2008**, *16*, 9133.

(12) Abouzid, K. A. M.; Khalil, N. A.; Ahmed, E. M.; Abd El-Latif, H. A.; El-Araby, M. E. *Med. Chem. Res.* **2010**, *19*, 629.

(13) Wagle, S.; Adhikari, A. V.; Kumari, N. S. *Eur. J. Med. Chem.* **2009**, *44*, 1135.

(14) Kleim, J. P.; Bender, R.; Billhardt, U. M.; Meichsner, C.; Riess, G.; Rösner, M.; Winkler, I.; Paessens, A. *Antimicrob. Agents Chemother.* **1993**, *37*, 1659.

(15) Kulkarni, N. V.; Revankar, V. K.; Kirasur, B. N.; Hugar, M. H. *Med. Chem. Res.* **2012**, *21*, 663.

(16) Amin, K. M.; Ismail, M. M. F.; Noaman, E.; Soliman, D. H.; Ammar, Y. A. *Bioorg. Med. Chem.* **2006**, *14*, 6917.

(17) Dailey, S.; Feast, J. W.; Peace, R. J.; Sage, I. C.; Till, S.; Wood, E. L. *J. Mater. Chem.* **2001**, *11*, 2238.

(18) Mizuno, T.; Wei, W.-H.; Eller, L. R.; Sessler, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 1134.

(19) Crossley, J. C.; Johnston, L. A. *Chem. Commun.* **2002**, 1122.

(20) (a) Gazit, A.; App, H.; McMahon, G.; Chen, J.; Levitzki, A.; Bohmer, F. D. *J. Med. Chem.* **1996**, *39*, 2170. (b) Sehlstedt, U.; Aich, P.; Bergman, J.; Vallberg, H.; Nordén, B.; Gräslund, A. *J. Mol. Biol.* **1998**, *278*, 31. (c) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439.

(21) (a) Eryazici, I.; Moorefield, C. N.; Durmus, S.; Newkome, G. R. *J. Org. Chem.* **2006**, *71*, 1009. (b) Tu, S. J.; Jia, R. H.; Jiang, B.; Zhang, J. Y.; Zhang, Y.; Yao, C. S.; Ji, S. J. *Tetrahedron* **2007**, *63*, 381.

(22) Sandeep, C.; Padmashali, B.; Kulkarni, R. S. *Tetrahedron Lett.* **2013**, *54*, 6411.

(23) Prasanna, P.; Kumar, S. V.; Gunasekaran, P.; Perumal, S. *Tetrahedron Lett.* **2013**, *54*, 3740.

(24) Wu, L.; Sun, J.; Yan, C.-G. *Org. Biomol. Chem.* **2012**, *10*, 9452.

(25) García Ruano, J. L.; Fraile, A.; Martín, M. R.; González, G.; Fajardo, C.; Martín-Castro, A. M. *J. Org. Chem.* **2011**, *76*, 3296.

(26) Moghaddam, F. M.; Khodabakhshi, M. R.; Ghahremannejad, Z.; Foroushani, B. K.; Ng, S. W. *Tetrahedron Lett.* **2013**, *54*, 2520.

(27) Matloubi Moghaddam, F.; Kiamehr, M.; Khodabakhshi, M. R.; Jebeli Javan, M.; Fathi, S.; Villinger, A.; Iaroshenko, V. O.; Langer, P. *Helv. Chim. Acta* **2013**, *96*, 2103.

(28) Matloubi Mogaddam, F.; Eslami, M.; Siahpoosh, A.; Golfam, H. *New J. Chem.* **2019**, *43*, 10318.

(29) Alizadeh, A.; Moafi, L. *Heterocycl. Commun.* **2017**, *23*, 375.

(30) Alizadeh, A.; Mohammadi, R.; Bayat, F.; Zhu, L. G. *Tetrahedron* **2017**, *73*, 4433.

(31) **1-Aryl-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene)ethanones 3; General Procedure**
NaOAc (1.5 mmol) was added to a solution of ninhydrin (1 mmol) and the appropriate phenylenediamine **1** (1 mmol) in EtOH (4 mL), and the solution was stirred for 1 h at r.t. Then, the appropriate 1-aryl-2-(triphenylphosphoranylidene)ethanone **4** (1.5 mmol) was added and the mixture was stirred at the reflux until the reaction was complete (TLC; 2 h). The mixture was then filtered and the product was recrystallized from EtOH.

(32) **Products 6a–o: General Procedure**
A mixture of isoquinoline (1 mmol) and the appropriate phenacyl bromide **5** (1 mmol) in CH_3CN (3 mL) was stirred at r.t. for 15 min. Et_3N (1 mmol) and the appropriate ketone **3** (1 mmol) were added, and the mixture was stirred under reflux until the reaction was complete (TLC; hexane–EtOAc, 1:2). The pure products was then simply collected by filtration and dried in air.
(2′-Benzoyl-2′,3′-dihydro-10b′*H*-spiro[indeno[1,2-*b*]quinoxaline-11,1′-pyrrolo[2,1-*a*]isoquinolin]-3′-yl)(4-tolyl)methanone (6b)
Orange solid; yield: 411 mg (69%); mp 207–209 °C. IR (KBr) = 1679, 1615, 14.99, 1460, 1328, 1238, 1130 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 2.41 (s, 3 H, CH_3), 5.23 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, CH pyrrolidine), 5.31 (d, $^3J_{HH}$ = 5.4 Hz, 1 H, olefinic CH), 5.36 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, N–CH pyrrolidine), 6.25–6.28 (t, $^3J_{HH}$ = 7.5 Hz, 1 H, H–Ar), 6.38 (s, 1 H, benzylic CH), 6.43 (d, $^3J_{HH}$ = 5.4 Hz, 1 H, olefinic CH–N), 6.53 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, H–Ar), 6.56–6.60 (t, $^3J_{HH}$ = 7.5 Hz, 2 H, H–Ar), 6.65 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, H–Ar), 6.70–6.75 (m, 3 H, H–Ar), 6.99–7.02 (t, $^3J_{HH}$ = 7.5 Hz, 1 H, H–Ar), 7.20–7.23 (t, $^3J_{HH}$ = 7.5 Hz, 1 H, H–Ar), 7.32 (d, $^3J_{HH}$ = 7.5 Hz, 3 H, H–Ar), 7.62 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, H–Ar), 7.78–7.81 (m, 3 H, H–Ar), 8.07 (d, $^3J_{HH}$ = 9.5 Hz, 1 H, H–Ar), 8.10 (d, $^3J_{HH}$ = 8.0 Hz, 2 H, H–

Ar), 8.32 (d, $^3J_{HH}$ = 9.4 Hz, 1 H, H–Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 21.7, 57.3, 65.3, 65.9, 69.8, 98.3, 121.2, 124.0, 124.1, 124.6, 126.1, 127.1, 127.2, 127.4, 127.6, 128.5, 128.9, 129.0, 129.1, 129.6, 129.7, 129.8, 130.9, 132.5, 132.8, 132.9, 134.0, 136.6, 137.3, 141.5, 142.2, 144.3, 144.7, 154.5, 160.4, 197.0, 197.4. Anal. calcd for $C_{41}H_{29}N_3O_2$ (595.70): C, 82.67; H, 4.91; N, 7.05. Found: C, 82.64; H, 4.96; N, 6.97.

Crystal Data for 6b: $C_{41}H_{29}N_3O_2$: M_W = 595.67, monoclinic, *P*21/*c*, *a* = 10.0450(8) Å, *b* = 17.0959(14) Å, *c* = 18.8967(15) Å, *β* = 104.646(2)°, *V* = 3139.7(4) Å^3, *Z* = 4, D_c = 1.293 mg/m^3, *F*(000) = 1281; crystal dimensions: 0.26 × 0.15 × 0.12 mm, radiation, Mo Kα (λ = 0.71073 Å), 3.424 ≤ 2*θ* ≤ 26.999, intensity data were collected at 123(2) K with a Bruker APEX area-detector diffractometer, employing the ω/2θ scanning technique, in the range –12 ≤ *h* ≤ 12, –21 ≤ *k* ≤ 21, –24 ≤ *l* ≤ 24. The structure was solved by a direct method; all nonhydrogen atoms were positioned and anisotropic thermal parameters were refined from 6837 observed reflections with $R_{(into)}$ = 0.0404 by a full-matrix least-squares technique converging to *R*1 = 0.0520, and w*R*2 = 0.1166 [*I* > 2σ(*I*)].

(33) CCDC 1949927 contains the supplementary crystallographic data for compound **6b**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.