JOC The Journal of Organic Chemistry

Article

Design of pyrazolo-pyrrolo-pyrazines and pyrazolo-pyrrolo-diazepines via AuCl3-catalyzed and NaH-supported cyclization of N-propargyl pyrazoles

Sinan Basceken, and Metin Balci

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 19 Mar 2015

Just Accepted

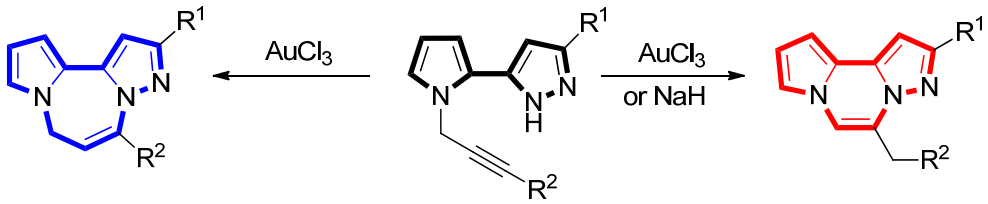
The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Design of pyrazolo-pyrrolo-pyrazines and pyrazolo-pyrrolo-diazepines via $AuCl_3$-catalyzed and NaH-supported cyclization of *N*-propargyl pyrazoles

Sinan Basceken,[†,‡] Metin Balci*,[†]

[†]Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey

[‡]Department of Chemistry, Hitit University, 19030 Corum, Turkey



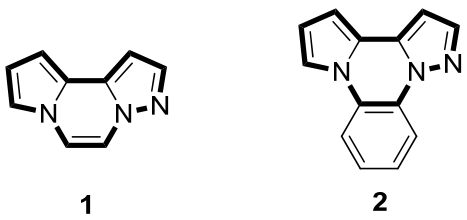
ABSTRACT: A concise synthetic methodology for a new heterocyclic scaffold such as a pyrazolo-pyrrolo-pyrazine and pyrazolo-pyrrolo-diazepine skeleton was developed. The key features of this method include: (i) the synthesis of pyrrole derived α,*β*-alkynyl ketones; (ii) introduction of various substituents into the alkyne functionality by Sonogashira cross-coupling; (iii) synthesis of pyrazole units by the reaction of α,*β*-alkynyl compounds with hydrazine monohydrate; (iv) gold-catalyzed cyclization of pyrazoles with alkyne units; and v) cyclization with NaH. Furthermore, this methodology allows to introduce various substituents into all positions of the target compounds.

Corresponding author's e-mail: mbalci@metu.edu.tr

Introduction

Heterocycles play a central role in the design of biologically active molecules and advanced organic materials. The synthesis of pyrazoles[1] has been extensively studied. Pyrazines[2] represent a class of particularly interesting heterocycles, due to their potential antiarrhythmic,[3] antiamnesic, antihypoxic,[4] psychotropic,[5] antihypersensitive,[6] and aldose reductase inhibition activities.[7]

Ring closure reactions in which a new carbon-heteroatom bond is formed are a common approach in the synthesis of heterocycles.[8] Specifically, the intramolecular addition of a nitrogen functionality to an alkyne or an alkene is a valuable strategy.[9] Herein, we report a synthetic methodology that enables efficient access to the important construction of five- and six-membered heterocyclic rings, such as pyrazoles and pyrazines, via intramolecular ring closure reactions.

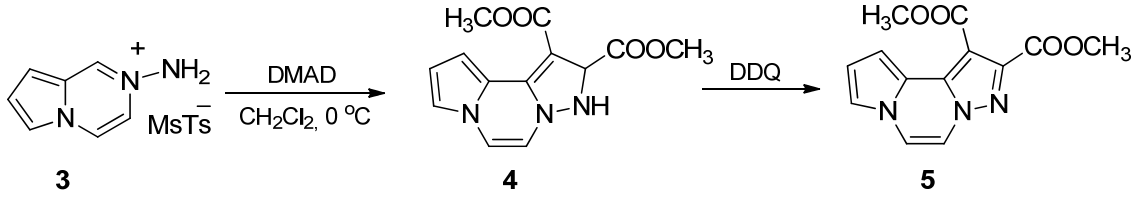


1 **2**

Figure 1. Structures **1** and **2**.

To the best of our knowledge, there is only one example of pyrazolo-pyrrolo-pyrazines **1** in the literature (Figure 1). 2-Aminopyrrolo[1,2-a]pyrazinium mesitylenesulfonate **3** was reacted with dimethyl acetylenedicarboxylate (DMAD) to give the dihydro derivative **4**, which was oxidized to **5** (Scheme 1).[10a] Surprisingly, a pyrazolo-pyrrolo-quinoxaline **2** skeleton, which is a benzo-derivative of **1**, has been generated as an unexpected product.[10b]

Scheme 1. Synthesis of 5 starting from 3.

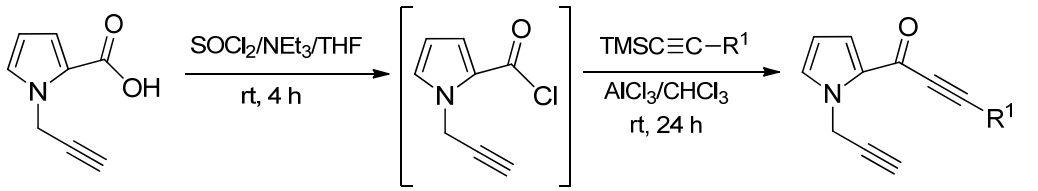


In this paper, we firstly illustrate the concept of cyclization of pyrrole-derived α,*β*-alkynyl ketones in the presence of hydrazine monohydrate and a subsequent gold(III)-catalyzed reaction[11] to provide practical synthetic access to the design of pyrazolo-pyrrolo-pyrazines **1**.

Results and Discussion

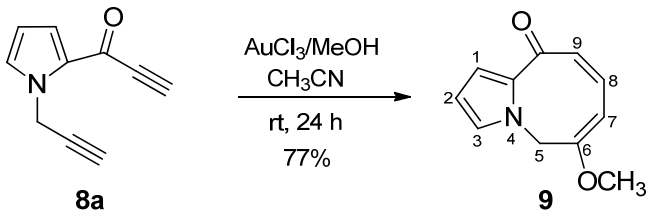
First, we investigated the feasibility of the intended synthetic approach to the target pyrazole scaffold exploring the reactivity of *N*-propargyl carboxylic acid **6**[12] for the synthesis of α,*β*–alkynyl ketones. The acid **6** was treated with thionyl chloride in the presence of triethylamine in THF at room temperature. The resulting acid chloride **7** was then condensed in situ with the substituted trimethylsilyl acetylenes to furnish the corresponding α,*β*-acetylenic ketones **8** (Scheme 2).

Scheme 2. Synthesis of alkyne-substituted pyrrole derivatives 8.



Although this work deals mainly with the synthesis of the title compound, pyrazolo-pyrrolo-pyrazines **1**, we reacted compound **8a** with $AuCl_3$ in a mixture of MeOH/CH_3CN at room temperature and observed the formation of an eight-membered heterocycle **9** in 77% yield after chromatographic purification (Scheme 3). The structure was assigned using 1D- and 2D-NMR spectra (DEPT, COSY, HSQC, and HMBC). In particular, the carbonyl carbon resonance at 191.1 ppm shows strong correlation with the olefinic proton H-8 (6.71 ppm) as well as with the pyrrole proton H-1 (6.77 ppm) over three bonds. On the other hand, the carbon resonance (C-6) at 155.2 ppm correlates with double bond protons H-8 (6.71 ppm), H-7 (5.52 ppm), and OCH_3 protons resonating at 3.77 ppm. Furthermore, the proton H-8 resonating at 6.72 ppm as doublet of doublets correlates with two olefinic protons H-9 and H-7 appearing at 5.91 and 5.52 ppm as doublets (COSY spectrum). All those findings support the proposed structure **9**.

Scheme 3. **Synthesis of (6*E*,8*Z*)-6-methoxypyrrolo[1,2-a]azocin-10(5*H*)-one (9)**

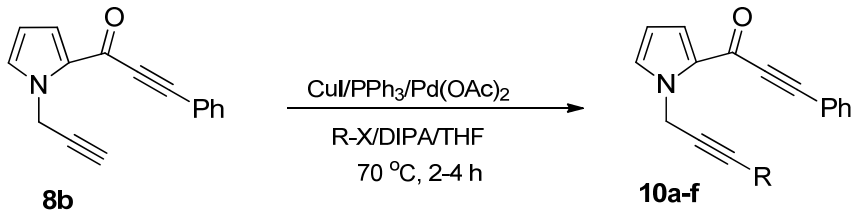


8a **9**

The next steps towards the substrate of the gold-catalyzed cyclization, was the synthesis of a library of dialkynyl ketones **10** with various substituents. The Sonogashira cross-coupling reaction[13] was used for the synthesis of the desired starting materials.

As revealed in Scheme 4, several halo-substituted aromatic compounds were coupled smoothly with alkyne derivatives **8b** to produce dialkynes **10**.

Scheme 4. **Synthesis of substituted dialkynes 10**



8b **10a-f**

	R-X	R	Yield (%)
a =	Ph-I	Ph	85
b =	*m*-NO_2-Ph-Br	*m*-NO_2-Ph-	80
c =	*p*-F-Ph-Br	*p*-F-Ph-	90
d =	*p*-CH_3Ph-Br	*p*-CH_3Ph-	92
e =	*p*-OMe-Ph-I	*p*-OMe-Ph-	83
f =	*o*-Pyr-Br	*o*-Pyr-	91

After the generation of substituted dialkynes **10** via the Sonogashira cross-coupling reaction we turned our attention to the synthesis of pyrazole derivatives **11**. Knorr pyrazole synthesis involving the condensation of a 1,3-dicarbonyl compounds with hydrazine is the most widely used method for pyrazole skeleton construction.[14] However, pyrazole synthesis by the condensation of pyropargyl ketones with hydrazines offers some advantages.[15] Even compounds with very sensitive functionalities can be readily constructed by a variety of acetylenic coupling reactions under very mild conditions.[16]

To our delight, *N*-propargyl α,*β*-alkynyl acetylenes **8a-c** and **10a-e** underwent a facile cyclization reaction with hydrazine, thus giving access to pyrazole-substituted pyrroles **11a-h** in 84-95% yields (Table 1). Interestingly, we found that hydrazine monohydrate reduces the pyrazole **11a** to **12** in the presence of air without any catalyst or metal (Scheme 5). We recently proposed that the oxygen dissolved in methanol was responsible for partial oxidation of hydrazine to diimide, which then reduced the triple and double bonds to the corresponding alkanes in high yields (Scheme 5).[17]

Scheme 5. **Reaction of 8a with hydrazine in the presence and absence of air**

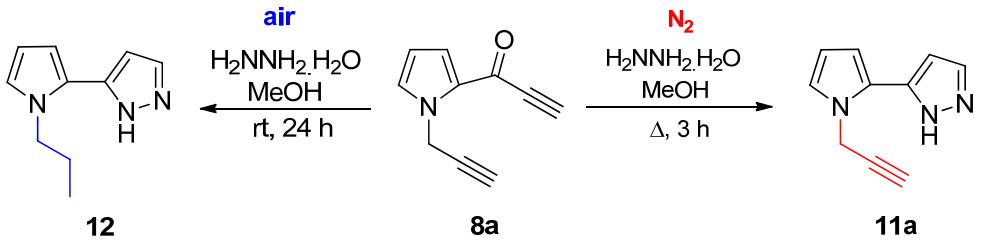
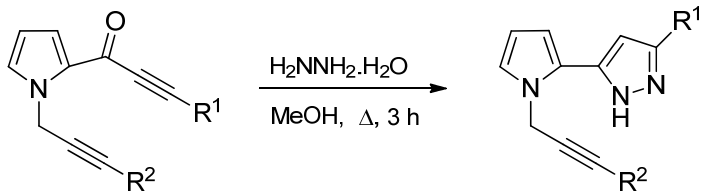
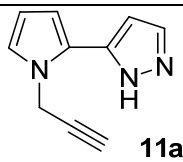
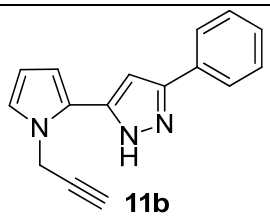
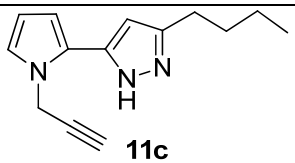
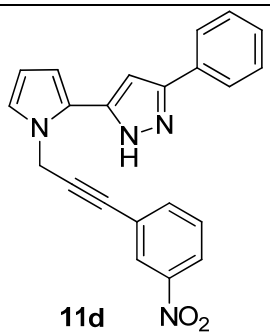
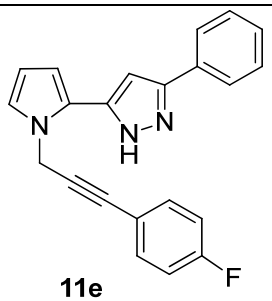
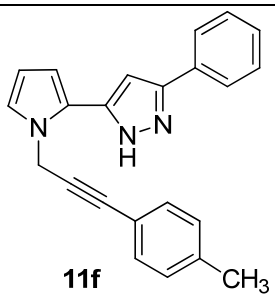
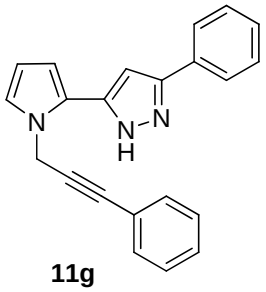
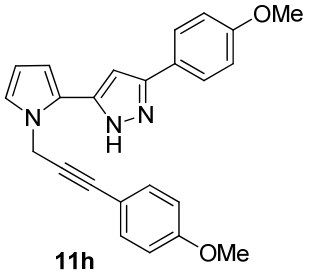


Table 1. Reaction of substituted 8 and 10 with hydrazine under nitrogen atmosphere to give 11



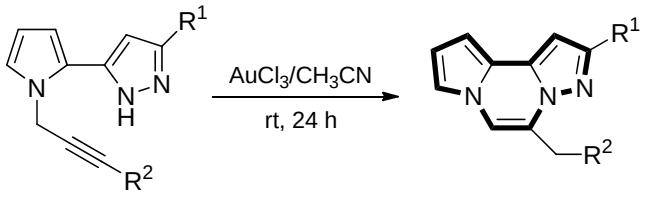
Entry[a]	R^1	R^2	Product	yields (%)[b]
1	H	H	 **11a**	85
2	Ph	H	 **11b**	95
3	*n*-Bu	H	 **11c**	92
4	Ph	*m*-NO_2Ph	 **11d**	94

5	Ph	*p*-FPh	 **11e**	84
6	Ph	*p*-CH_3Ph	 **11f**	90
7	Ph	Ph	 **11g**	95
8	*p*-OMePh	*p*-OMePh	 **11h**	88

[a]Reaction conditions: Ketones (0.5 mmol), hydrazine monohydrate (1 mL), MeOH (15 ml), 70 °C, 3 h. [b]Isolated yields, %.

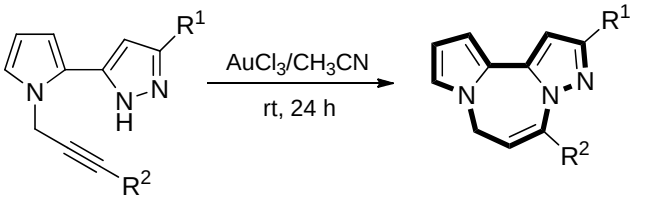
We envisioned that the metal-catalyzed intramolecular cyclization reaction between pyrazoles and alkynes might provide an entry to the facile synthesis of pyrazolo-pyrrolo-pyrazine **13**[18] and pyrazolo-pyrrolo-diazepine systems **14**

Table 2. **Intramolecular cyclization of 11a-h with $AuCl_3$ and NaH to produce 13 and 14**



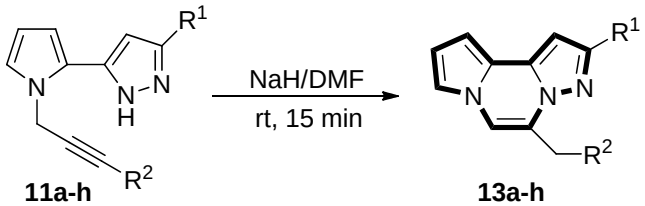
11a-c **13a-c**

	R^1	R^2
a	H	H
b	Ph	H
c	*n*-Bu	H

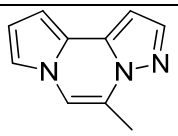
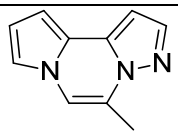
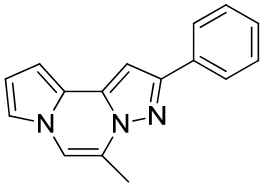
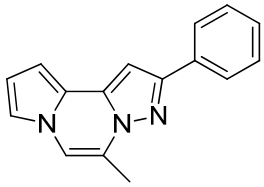
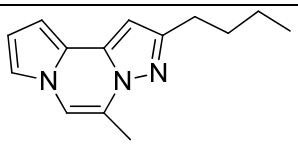
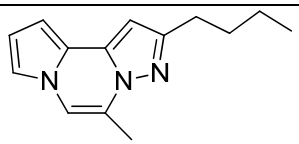


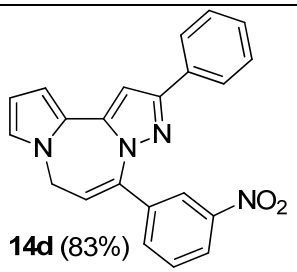
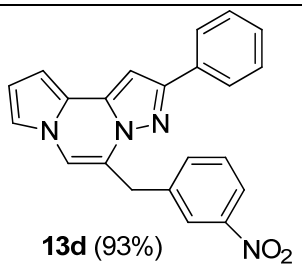
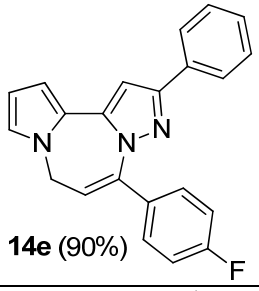
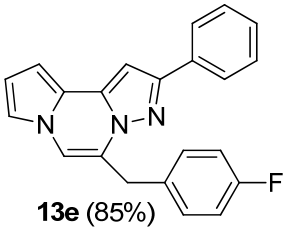
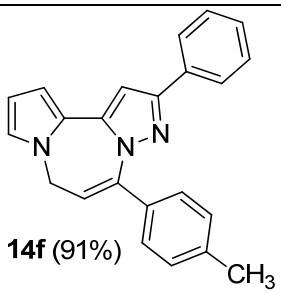
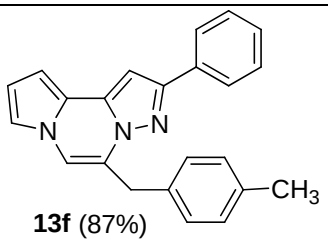
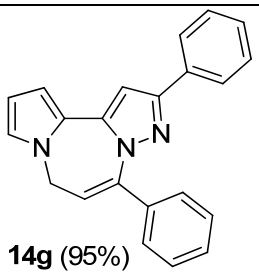
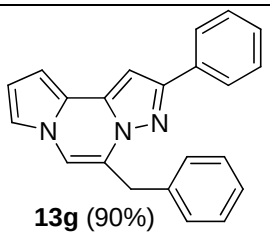
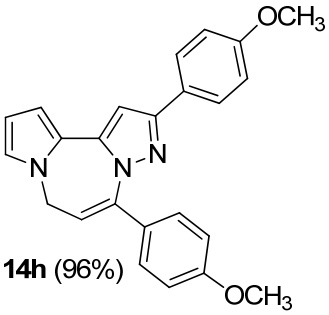
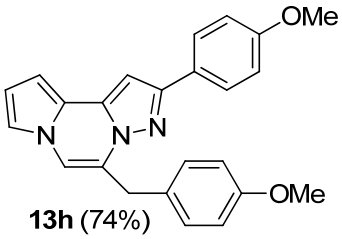
11d-h **14d-h**

	R^1	R^2
d	Ph	*m*-NO_2Ph
e	Ph	*p*-FPh
f	Ph	*p*-CH_3Ph
g	Ph	Ph
h	*p*-OMePh	*p*-OMePh



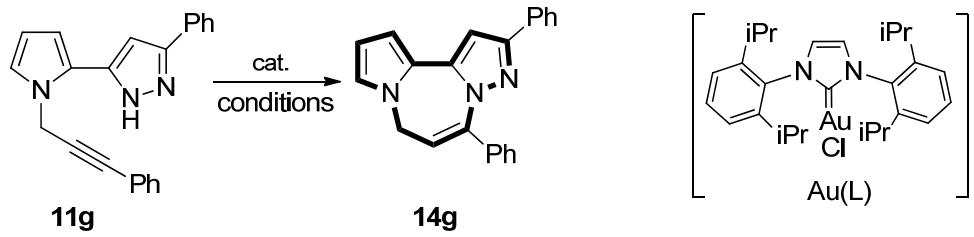
11a-h **13a-h**

entry	Product by $AuCl_3$-catalyzed cyclization (yields)	Product by NaH-promoted cyclization (yields)
1	 **13a** (75%)	 **13a** (95%)
2	 **13b** (80%)	 **13b** (91%)
3	 **13c** (70%)	 **13c** (87%)

4	 **14d** (83%)	 **13d** (93%)
5	 **14e** (90%)	 **13e** (85%)
6	 **14f** (91%)	 **13f** (87%)
7	 **14g** (95%)	 **13g** (90%)
8	 **14h** (96%)	 **13h** (74%)

Seven different catalysts were tried (Table 3). Surprisingly, no reaction was observed when the reaction was conducted with CuOTf, N-heterocyclic carbene (NHC) complex of Au(I), and $PtCl_2(PPh_3)_3$ in acetonitrile (Table 1, entries 1, 2, and 3). Reactions with $InCl_3$ and AgOTf gave trace amount of cyclization product after 24 h (Entries 4 and 5). However, reactions with AuCl and $AuCl_3$ catalysts gave *endo*-dig cyclization product **14g** after 3 h (Entries 6 and 7) in yields of 93% and 95%, respectively.

Table 3. Catalyst Screening on the Cyclization Reaction of 11g



11g **14g**

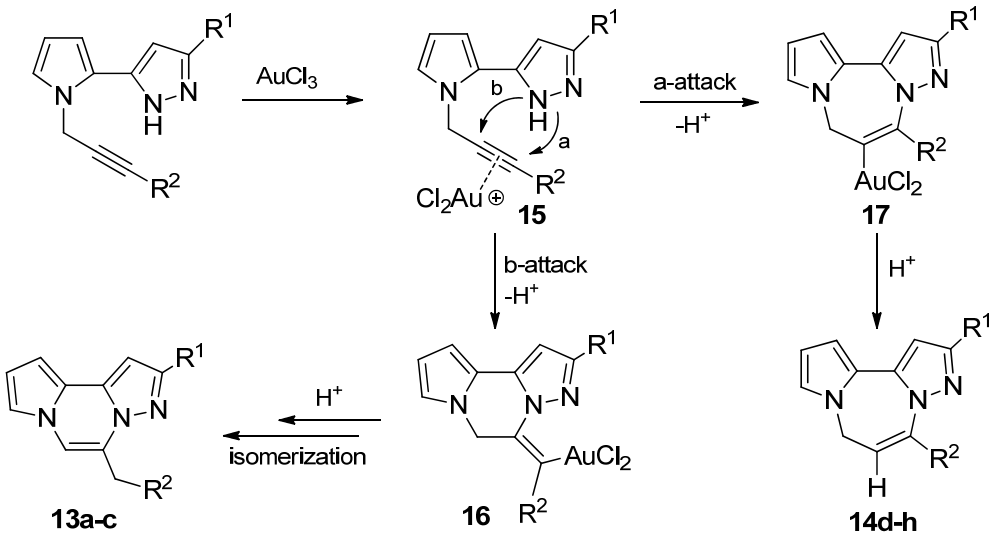
entry	catalyst	solvent	condition	result
1	CuOTf	CH_3CN	24 h, rt	no reaction
2	$PdCl_2(PPh_3)_2$	CH_3CN	24 h, rt	no reaction
3	Au(L)	CH_3CN	24 h, rt	no reaction
4	AgOTf	CH_3CN	24 h, rt	trace
5	$InCl_3$	CH_3CN	24 h, rt	trace
6	AuCl	CH_3CN	3 h, rt	93%
7	$AuCl_3$	CH_3CN	3 h, rt	95%

After having obtained the optimal condition for the Au-catalyzed cyclization of **11g**, we attempted to determine the scope and limitation of this transformation. To test our strategy, we reacted pyrazoles **11a-c** having terminal alkynes with $AuCl_3$ at room temperature to afford the pyrazolo-pyrrolo-pyrazines **13a-c** in good-to-excellent yields (Table 2, entries 1-3). The reaction proceeds via electrophilic activation of the triple bond followed by 6-*exo*-*dig* heterocyclization and H-shift leading to the pyrazolo-pyrrolo-pyrazine systems **13a-c**. However, the reaction of substituted alkynes **11d-h**, under the same reaction conditions, underwent smooth 7-*endo*-*dig* cyclization[19] to produce **14d-h** having a pyrazolo[1,5-*a*]pyrrolo[2,1-*c*][1,4]diazepine skeleton.[20]

The structures of those cyclization products **13** and **14** were determined by 1D and 2D NMR (COSY, HSQC, and HMBC) spectra. The exact location of the methylene group in **13g** was established from the HMBC spectrum, which showed a strong correlation between the methylene carbon appearing at 34.5 ppm with two *o*-protons of the benzene ring and double bond proton in pyrazine ring, indicating clearly that methylene protons are located between the double bond and the benzene ring. However, in the case of **14g**, methylene carbon shows correlation with the double bond proton as well as with the pyrrole proton clearly showing that the methylene group is directly attached to the nitrogen atom of pyrrole.

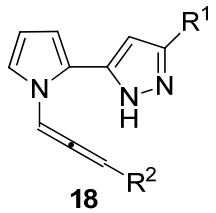
The formation of 7-*endo-dig* cyclization products **14d-h** can be explained first by the activation of the alkyne unit with gold cation where the positive charge is closer to the aromatic ring because of the better stabilization.[19] The so-generated π-complex undergoes intramolecular nucleophilic attack by the nitrogen atom of the pyrazole group, affording the seven-membered ring.

Scheme 6. Proposed reaction mechanism for the intramolecular gold-catalyzed cyclization reactions to form 13 and 14.



Based on all this information obtained, we propose the following gold-catalyzed cyclization reaction mechanism (Scheme 6). The proposed catalytic cycle was initiated with π-activation of the triple bond by $AuCl_3$ to form the intermediate **15**, which triggers a gold-promoted intramolecular addition of NH group of pyrazole to the alkyne functionality to give the intermediates **16** and **17**. The electronic nature of the substituents attached to the triple bond determines the mode of the nucleophilic attack. In the next step, gold species is removed by proton to give the final products **13** and **14**.

After successful cyclization of pyrazole derivatives with $AuCl_3$ giving 7-*endo-dig* as well as 6-*exo-dig* products we turned our attention to intramolecular ring-cyclization reactions of **11a-h** with NaH. The reaction of **11a-h** with NaH in *N,N*-dimethylformamide (DMF) at room temperature gave exclusively 6-*exo-dig* heterocyclization products **13a-h**. We assume that the alkyne functionality first undergoes a base-catalyzed isomerization to give the corresponding allenes **18** (Figure 2).[12] Since the central carbon atom in the allene moiety is more electropositive, a nitrogen atom from the pyrazole ring attacks exclusively this carbon atom giving rise to the formation of 6-*exo-dig* cyclization products **13** (Table 2).



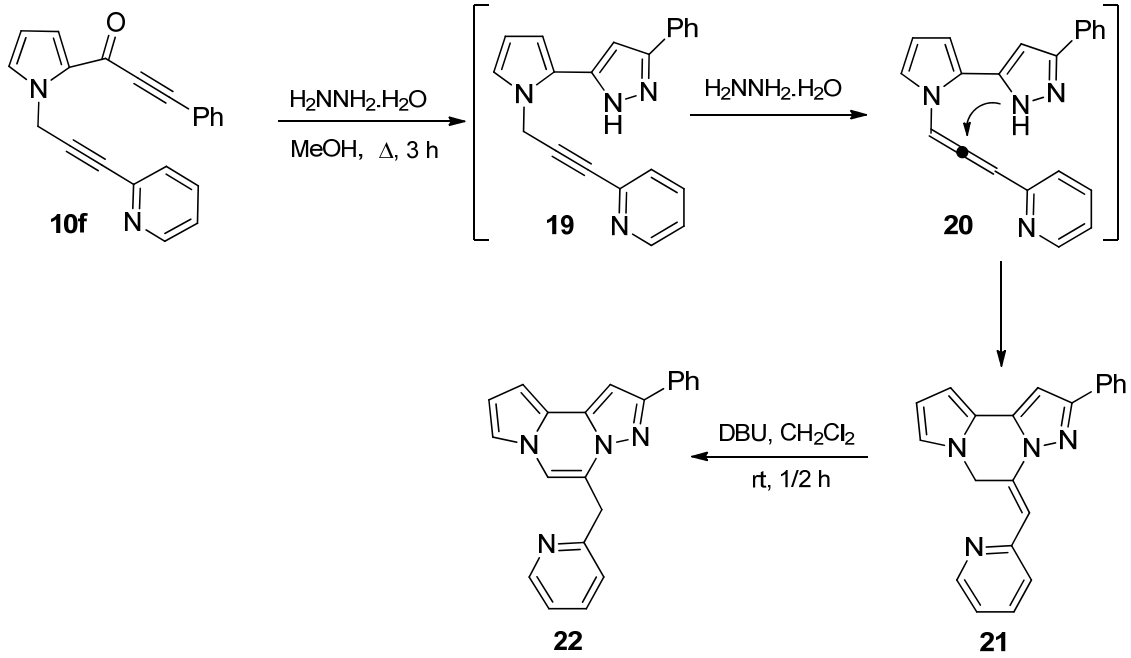
18

Figure 2. The structure of the intermediate **18** formed during cyclization with NaH.

It was interesting to observe that **10f** did not form the expected pyrazole derivative **18** having acetylene units. The ^{13}C-NMR spectrum of the product showed that the acetylene carbon resonances were absent. The NMR spectra of the isolated product were in agreement with the

cyclization product **21** with *exo*-methylene unit (Scheme 7). Probably hydrazine acts as a base and isomerizes the alkyne unit in **19** to the corresponding allene **20**, which undergoes an intramolecular 6-*exo*-trig cyclization reaction to give the isolated product **21**.[21] We assume that the pyridine ring, an electron deficient aromatic ring, is responsible for isomerization of the alkyne unit into the corresponding allene moiety. The NMR spectra of **21** supported the proposed structure. The isomerization of **21** into **22** was accomplished with DBU at room temperature in high yield. The spectral data of **22** were in complete agreement with the proposed structure. Finally, the structure of **22** was further confirmed by single crystal X-ray analysis (See Supporting information).

Scheme 7. **Reaction of 10f with hydrazine and synthesis of 21 and 22.**



Conclusion

We have developed a concise synthetic methodology for a new heterocyclic scaffold such as a pyrazolo-pyrrolo-pyrazine skeleton **13** as well as pyrazolo-pyrrolo-diazepine skeleton **14**. The key features of this method include: (i) the synthesis of pyrrole derived α,*β*-alkynyl ketones; (ii) introduction of various substituents into the alkyne functionality by Sonogashira cross-coupling; (iii) synthesis of pyrazole units by the reaction of α,*β*-alkynyl compounds with hydrazine monohydrate; (iv) gold-catalyzed cyclization of pyrazoles with alkyne units; and v) cyclization with NaH. This synthetic strategy represents a reasonable methodology for the construction of hitherto unknown skeleton, pyrazolo-pyrrolo-diazepine and pyrazolo-pyrrolo-pyrazine in high yield. Furthermore, this methodology will allow us to introduce various substituents into all positions of the target compound.

Experimental Section

General Methods. All reagents were used as purchased from commercial suppliers without further purification. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on an instrument 400 MHz and chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ as an internal standard. The ^{13}C-NMR spectra were recorded on an instrument 100 MHz and are reported in ppm using solvent as an internal standard ($CDCl_3$. Column chromatography was performed on silica gel (60-mesh). TLC was carried out on 0.2 mm silica gel 60 F254 analytical aluminum plates. High resolution Mass spectra were recorded by LC-MS TOF electrospray ionization technique. Chemicals and all solvents were commercially available and used without further purification. Infrared (IR) spectra were recorded in the range 4000-600 cm-1 via ATR diamond. Melting points were measured using melting point apparatus

and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

1-(Prop-2-yn-1-yl)-1H-pyrrole-2-carboxylic acid (***6***):[17] To a solution of methyl 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxylate (1.0 g, 6.13 mmol) in methanol (3 mL) a solution of methanol/water (1:1) (60 mL) and K_2CO_3 (15 g) was added. The reaction mixture was refluxed for 24 h. After cooling to room temperature, the mixture was acidified with 3 *N* hydrochloric acid in an ice bath for 15 min, and extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and evaporated to give 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxylic acid (**6**) as colorless crystals (95%, 5.82 mmol, 0.87 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.12 (m, 1H, CH), 7.07 (dd, J = 4.0 and 1.8 Hz, 1H, CH), 6.15 (dd, J = 4.0 and 2.7 Hz, 1H, CH), 5.10 (d, J = 2.6 Hz, 2H, CH_2), 2.38 (t, J = 2.6 Hz, 1H, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 127.3, 119.1, 118.9, 107.2, 76.1, 72.2, 36.5.

1-(1-(Prop-2-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-one (***8a***): To a solution of 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxylic acid (**6**) (500 mg, 3.35 mmol) in THF (20 mL) was added triethylamine (100 μL, 0.7 mmol). The reaction mixture was stirred at room temperature for 0.5 h. To this solution was then added a solution of thionyl chloride (800 μL, 11 mmol) in THF (2 mL) dropwise, and the resulting mixture was stirred at room temperature for 3 h. Afterwards the solid was filtered off, and solvent was evaporated. The acyl chloride was dissolved in chloroform (5 mL) without purification, and trimethylsilyl acetylene (480 μL, 1.0 equiv.) was added to the solution at room temperature. The mixture was then added to a solution of aluminum chloride (450 mg, 3.4 mmol) in chloroform (15 mL) dropwise at 0 °C, and the mixture was stirred for 24 h at room temperature. After completion of the reaction (controlled by TLC), water (30 mL) was added, and the solution was extracted with ethyl acetate. The combined organic extracts were

dried over Na_2SO_4. The solvent was evaporated to give crude product, which was purified by column chromatography eluting with EtOAc/hexane to give **8a** as colorless crystals (65%, 1.82 mmol, 0.29 g) mp 81-83 °C. R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (ddd, J = 5.8, 4.1 and 1.8 Hz, 2H, CH), 6.17 (dd, J = 4.1 and 2.6 Hz, 1H, CH), 5.10 (d, J = 2.6 Hz, 2H, CH_2), 3.13 (s, 1H, C≡CH), 2.41 (t, J = 2.6 Hz, 1H, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 130.3, 129.9, 124.4, 108.9, 79.9, 76.4, 75.9, 73.7, 37.8; IR (ATR, cm^{-1}) 3259, 3107, 2915, 2121, 2097, 1608, 1463, 1395, 1335, 1235, 1059, 975, 939, 736, 654; HRMS Calcd for ($C_{10}H_7NO$) $[M + H]^+$: 158.06004; Found: 158.05972.

*3-Phenyl-1-(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-one (**8b**):* To a solution of 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxylic acid (**6**) (500 mg, 3.35 mmol) in THF (20 mL) was added triethylamine (100 μL, 0.7 mmol). The reaction mixture was stirred at room temperature for 0.5 h. To this solution was then added a solution of thionyl chloride (800 μL, 11 mmol) in THF (2 mL) dropwise, and the resulting mixture was stirred at room temperature for 3 h. Afterwards the solid was filtered off, and solvent was evaporated. The acyl chloride was dissolved in chloroform (5 mL) without purification, and trimethyl(phenylethynyl)silane[20] (580 mg, 1.0 equiv.) was added to the solution at room temperature. The mixture was then added to a solution of aluminum chloride (450 mg) in chloroform (15 mL) dropwise at 0 °C, and the mixture was stirred for 24 h at room temperature. After completion of the reaction (controlled by TLC), water (30 mL) was added, and the solution was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4. The solvent was evaporated to give crude product, which was purified by column chromatography eluting with EtOAc/hexane to give **8b** as a brown colored solid (70%, 2.68 mmol, 625 mg), mp 79-81 °C. R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.47 (m, 2H, CH), 7.37-7.25 (m, 3H, CH), 7.24 (dd, J = 4.1 and 1.7 Hz, 1H, CH), 7.20-7.17 (m, 1H, CH), 6.17 (dd, J = 4.1 and 2.6 Hz, 1H, CH), 5.14 (d, J = 2.6 Hz, 2H, CH_2), 2.39 (t, J = 2.6 Hz, 1H, C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 132.9, 131.4, 130.8, 130.3, 128.6, 124.6, 120.6, 109.8, 89.1, 87.5, 77.7, 74.6, 38.8; IR (ATR, cm^{-1}) 3059, 2983, 2200, 2121, 1607, 1401,

1332, 1266, 1214, 1076, 1050, 984, 746, 728, 686; HRMS Calcd for ($C_{16}H_{11}NO$) $[M + H]^+$: 234.09134; Found: 234.09136.

*1-(1-(Prop-2-yn-1-yl)-1H-pyrrol-2-yl)hept-2-yn-1-one (**8c**).* To a solution of 1-(prop-2-yn-1-yl)-1*H*-pyrrole-2-carboxylic acid (**6**) (500 mg, 3.35 mmol) in THF (20 mL) was added triethylamine (100 μL, 0.7 mmol). The reaction mixture was stirred at room temperature for 0.5 h. To this solution was then added a solution of thionyl chloride (800 μL, 11 mmol) in THF (2 mL) dropwise, and the resulting mixture was stirred at room temperature for 3 h. Afterwards the solid was filtered off, and solvent was evaporated. The acyl chloride was dissolved in chloroform (5 mL) without purification, and hex-1-yn-1-yltrimethylsilane (517 mg, 1.0 equiv.) was added to the solution at room temperature. The mixture was then added to a solution of aluminum chloride (450 mg,) in chloroform (15 mL) dropwise at 0 °C, and the mixture was stirred for 24 h at room temperature. After completion of the reaction (controlled by TLC), water (30 mL) was added, and the solution was extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4. The solvent was evaporated to give crude product, which was purified by column chromatography eluting with EtOAc/hexane to give **8c** as a colorless viscous liquid (67%, 2.24 mmol, 478 mg). R_f = 0.7 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-7.02 (m, 1H, CH), 6.99 (dd, J = 4.1 and 1.8 Hz, 1H, CH), 6.02 (dd, J = 4.1 and 2.6 Hz, 1H, CH), 5.01 (d, J = 2.5 Hz, 1H, CH_2), 2.26 (t, J = 2.6 Hz, 1H, C≡CH), 2.23 (t, J = 7.0 Hz, 2H, CH_2), 1.47-1.37 (m, 2H, CH_2), 1.28 (hextet, J = 7.1 Hz, 1H, CH_2), 0.75 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 131.7, 130.6, 124.5, 109.7, 92.6, 80.3, 77.9, 74.6, 38.9, 30.1, 22.3, 18.9, 13.8; IR (ATR, cm^{-1}) 2962, 2931, 2868, 2240, 2203, 1605, 1403, 1348, 1233, 1111, 1076, 901, 865, 733; HRMS Calcd for ($C_{14}H_{15}NO$) $[M + H]^+$: 214.12264; Found: 214.12276.

*(6E,8Z)-6-Methoxypyrrolo[1,2-a]azocin-10(5H)-one (**9**).* To a solution of 1-(1-(prop-2-yn-1-yl)-1*H*-pyrrol-2-yl)prop-2-yn-1-one (**8a**) (100 mg, 0.64 mmol) in acetonitrile (4 mL) was added gold trichloride (2.5 mmol%, 5 mg) in acetonitrile (1 mL) dropwise at room temperature. The reaction mixture suddenly becomes dark red, and then methanol (100 μL) was added. The

resulting mixture was stirred at room temperature for 24 h. The crude product was chromatographed on a silica gel column eluting with EtOAc/hexane to give **9** as an yellow-colored solid. (77%, 0.49 mmol, 0.09 g), mp 119-120 °C. R_f = 0.5 (ethyl acetate/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80-6.75 (m, 1H, CH), 6.72 (dd, J = 12.8 and 8.4 Hz, 1H, CH), 6.48 (dd, J = 3.8 and 1.7 Hz, 1H, CH), 6.25 (dd, J = 3.8 and 2.7 Hz, 1H, CH), 5.91 (d, J = 12.8 Hz, 1H, CH), 5.52 (d, J = 8.4 Hz, 1H, CH), 4.64 (d, J = 13.4 Hz, 1H, CH), 4.37 (d, J = 13.4 Hz, 1H, CH), 3.77 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 155.2, 138.8, 126.9, 125.9, 121.9, 110.1, 109.7, 97.3, 54.9, 54.1; IR (ATR, cm^{-1}) 3116, 2916, 2848, 1652, 1554, 1524, 1441, 1416, 1223, 1156, 1078, 957, 758; HRMS Calcd for ($C_{11}H_{11}NO_2$) $[M + H]^+$: 190.08626; Found: 190.08655.

General Procedure for Sonogashira Coupling. A stirred mixture of CuI (17 mg, 0.09 mmol), PPh_3 (90 mg, 0.34 mmol), and $Pd(OAc)_2$ (17 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of α,β-acetylenic ketones (1.1 mmol), halide arenes (1.2 mmol), and DIPA (2 mL) in THF (15 mL) was added successively. The mixture was then refluxed for 2-4 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane to give pure product.

*3-Phenyl-1-(1-(3-phenylprop-2-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-one (**10a**).* A yellow colored solid (85%, 0.94 mmol, 289 mg), mp 76-78 °C. R_f = 0.5 (ethyl acetate/hexane, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.1, 1.4 Hz, 2H), 7.46 – 7.19 (m, 11H), 6.21 (dd, J = 4.0, 2.6 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 132.8, 131.9, 131.5, 130.8, 130.2, 128.7, 128.6, 128.3, 124.6, 122.3, 120.7, 109.6, 88.9, 87.5, 86.3, 82.9, 39.7; IR (ATR, cm^{-}

^{1}) 2974, 2913, 2846, 2199, 1604, 1402, 1352, 1266, 1214, 1074, 1049, 971; HRMS Calcd for ($C_{22}H_{15}NO$) $[M + H]^+$: 310.12264; Found: 310.12365.

*1-(1-(3-(3-Nitrophenyl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)-3-phenylprop-2-yn-1-one (**10b**).* A yellow colored solid (80%, 0.88 mmol, 312 mg), mp 100-102 °C. R_f = 0.4 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.24 (m, 1H), 8.17 (ddd, J = 8.3, 2.2, 1.0 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.67 – 7.59 (m, 2H), 7.54 – 7.26 (m, 7H), 6.31 (dd, J = 4.1, 2.6 Hz, 1H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 148.1, 137.5, 132.8, 131.5, 130.9, 130.4, 129.4, 128.6, 126.7, 124.6, 124.1, 123.4, 120.5, 109.9, 89.3, 87.4, 85.9, 83.3, 39.4; IR (ATR, cm^{-1}) 3083, 2919, 2850, 2196, 1609, 1526, 1407, 1345, 1053, 981, 729; HRMS Calcd for ($C_{22}H_{14}N_2O_3$) $[M + H]^+$: 355.10772; Found: 355.10946.

*1-(1-(3-(4-Fluorophenyl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)-3-phenylprop-2-yn-1-one (**10c**).* A yellow colored solid (90%, 0.99 mmol, 324 mg), mp 83-84 °C. R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.38 – 7.29 (m, 7H), 6.93 (t, J = 8.7 Hz, 2H), 6.23 – 6.19 (m, 1H), 5.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 161.59 (d, $J_{C,F}$ = 248 Hz), 132.65 (d, $J_{C,F}$ = 8 Hz), 131.6, 130.4, 129.6, 129.1, 127.4, 123.4, 119.5, 117.2, 114.48 (d, $J_{C,F}$ = 22 Hz), 108.5, 87.9, 86.4, 83.9, 81.6, 38.4; IR (ATR, cm^{-1}) 2989, 2962, 2917, 2196, 1611, 1503, 1402, 1350, 1220, 1050, 974, 833, 750, 727, 683; HRMS Calcd for ($C_{22}H_{14}FNO$) $[M + H]^+$: 328.11322; Found: 328.11648

*3-Phenyl-1-(1-(3-(p-tolyl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-one (**10d**).* A yellow colored solid, (95%, 1.04 mmol, 336 mg), mp 94-96 °C. R_f = 0.7 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 2H), 7.43-7.32 (m, 7H), 7.09 (d, J = 8.1 Hz, 2H), 6.26 (dd, J = 4.0, 2.6 Hz, 1H), 5.43 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 138.9, 132.8, 131.8, 131.5, 130.9, 130.3, 129.1, 128.6, 124.6, 120.7, 119.2, 109.6, 89.0, 87.6, 86.5, 82.2,

39.8, 21.5; IR (ATR, cm^{-1}) 2985, 2970, 2899, 2196, 1607, 1407, 1349, 1049; HRMS Calcd for ($C_{23}H_{17}NO$) $[M + H]^+$: 324.13829; Found: 324.13612.

*3-(4-Methoxyphenyl)-1-(1-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-one (**10e**).* A yellow colored solid (83%, 0.91 mmol, 337 mg), mp 102-104 °C. R_f = 0.4 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.53 (m, 2H), 7.42 – 7.36 (m, 3H), 7.33 (dd, J = 4.0, 1.7 Hz, 1H), 6.94 – 6.87 (m, 2H), 6.86 – 6.78 (m, 2H), 6.27 (dd, J = 4.0, 2.6 Hz, 1H), 5.45 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 161.3, 159.9, 134.7, 133.3, 131.6, 130.6, 124.2, 114.3, 113.9, 112.5, 109.4, 89.9, 87.2, 86.2, 81.6, 55.4, 55.3, 39.8; IR (ATR, cm^{-1}) 2917, 2847, 2194, 1593, 1506, 1400, 1246, 1022, 826; HRMS Calcd for ($C_{24}H_{19}NO_3$) $[M + H]^+$: 370.14377; Found: 370.14424.

*3-Phenyl-1-(1-(3-(pyridin-2-yl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-one (**10f**).* A yellow viscous liquid (91%, 1.0 mmol, 311 mg). R_f = 0.4 (ethyl acetate/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.55 (m, 1H), 7.64 (m, 3H), 7.49 – 7.33 (m, 6H), 7.24 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H), 6.28 (dd, J = 4.1, 2.6 Hz, 1H), 5.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 150.0, 142.5, 136.2, 132.8, 131.5, 131.1, 130.3, 128.7, 127.4, 124.6, 123.3, 120.6, 109.9, 89.1, 87.5, 85.3, 83.0, 39.3; IR (ATR, cm^{-1}) 2986, 2901, 2197, 1593, 1579, 1463, 1401, 1269, 1045, 750, 728; HRMS Calcd for ($C_{21}H_{14}N_2O$) $[M + H]^+$: 311.11789; Found: 311.12187.

General procedure for the synthesis of pyrazoles. To a refluxing solution of methanol (15 mL) and ketones **8a-c/10a-e** (0.5 mmol) was added hydrazine monohydrate (1 mL) dropwise at 70 °C under nitrogen atmosphere. Refluxing was continued for 3 h, water was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined extracts were dried over Na_2SO_4, and evaporated. The crude product was chromatographed on silica gel eluting with ethyl acetate/hexane to give pyrazole derivatives.

*5-(1-(Prop-2-yn-1-yl)-1H-pyrrol-2-yl)-1H-pyrazole (**11a**).* A light yellow viscous liquid (85%, 0.43 mmol, 73 mg). R_f = 0.5 (ethyl acetate/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (bs, 1H), 7.49 (d, J = 2.1 Hz, 1H), 6.86 (dd, J = 2.7, 1.8 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 6.36 (dd, J = 3.7, 1.8 Hz, 1H), 6.20 – 6.13 (m, 1H), 4.91 (d, J = 2.5 Hz, 2H), 2.31 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 131.3, 124.0, 121.8, 108.8, 107.8, 103.3, 78.1, 72.3, 36.4; IR (ATR, cm^{-1}) 3273, 3159, 2916, 2902, 2845, 1712, 1614, 1580, 1435, 1401, 1111, 1072, 934, 791, 678; HRMS Calcd for ($C_{10}H_9N_3$) $[M + H]^+$: 172.08692; Found: 172.08650.

*3-Phenyl-5-(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)-1H-pyrazole (**11b**).* A light yellow viscous liquid (95%, 0.48 mmol, 117 mg). R_f = 0.6 (ethyl acetate/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.67 (m, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.38 – 7.31 (m, 1H), 6.95 (dd, J = 2.7, 1.8 Hz, 1H), 6.73 (s, 1H), 6.45 (dd, J = 3.6, 1.8 Hz, 1H), 6.27 – 6.23 (m, 1H), 4.96 (d, J = 2.5 Hz, 2H), 2.41 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 134.9, 131.1, 128.9, 128.8, 128.4, 125.6, 123.0, 109.9, 108.9, 101.8, 78.9, 73.6, 37.4; IR (ATR, cm^{-1}) 3289, 3153, 3104, 3065, 3016, 2919, 1690, 1605, 1581, 1456, 1283, 1073, 966, 762, 717, 690; HRMS Calcd for ($C_{16}H_{13}N_3$) $[M + H]^+$: 248.11822; Found: 248.11809.

*3-Butyl-5-(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)-1H-pyrazole (**11c**).* A light yellow viscous liquid (92%, 0.46 mmol, 105 mg). R_f = 0.4 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, J = 2.6, 1.9 Hz, 1H), 6.29 (dd, J = 3.6, 1.9 Hz, 1H), 6.18 – 6.07 (m, 2H), 4.93 (d, J = 2.5 Hz, 2H), 2.58 – 2.45 (t, J = 7.7 Hz, 2H), 2.28 (t, J = 2.5 Hz, 1H), 1.53 (quintet, J = 7.5 Hz, 2H), 1.28 (hextet, J = 7.5 Hz, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 135.0, 125.8, 122.4, 109.4, 108.6, 102.6, 79.2, 73.2, 37.4, 31.3, 25.9, 22.3, 13.8; IR (ATR, cm^{-1}) 3286, 3189, 3098, 2955, 2929, 2860, 1584, 1466, 1273, 1068, 944, 786, 712; HRMS Calcd for ($C_{14}H_{17}N_3$) $[M + H]^+$: 228.14952; Found: 228.15039.

5-(1-(3-(3-Nitrophenyl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)-3-phenyl-1H-pyrazole ***(11d)***. A yellow colored solid (94%, 0.47 mmol, 173 mg), mp 117-118 °C. R_f = 0.6 (ethyl acetate/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.08 (m, 2H), 7.63 (d, J = 6.9 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.39 – 7.27 (m, 4H), 6.96 (s, 1H), 6.72 (s, 1H), 6.49 – 6.41 (m, 1H), 6.26 (dd, J = 3.6, 1.8 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 148.0, 143.0, 137.9, 131.2, 129.8, 129.5, 128.9, 127.1, 126.2, 125.3, 124.6, 123.8, 123.6, 110.6, 109.6, 102.4, 87.6, 83.2, 38.6; IR (ATR, cm^{-1}) 3101, 3074, 2968, 2913, 1581, 1525, 1348, 1280, 1073, 944, 802, 761,717; HRMS Calcd for ($C_{22}H_{16}N_4O_2$) $[M + H]^+$: 369.13460; Found: 369.13714.

5-(1-(3-(4-Fluorophenyl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)-3-phenyl-1H-pyrazole ***(11e)***. A light yellow viscous liquid (84%, 0.42 mmol, 143 mg). R_f = 0.4 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (bs, 1H), 7.69 (d, J = 7.1 Hz, 2H), 7.46 – 7.35 (m, 5H), 7.01-7.02 (m, 1H), 6.99-6.95 (J = 8.6, Hz, 2H), 6.74 (s, 1H), 6.45 (dd, J = 3.6, 1.7 Hz, 1H), 6.31 – 6.20 (m, 1H), 5.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.68 (d, $J_{C,F}$ = 248 Hz), 148.3, 141.4, 133.73 (d, $J_{C,F}$ = 9 Hz), 131.2, 128.9, 128.3, 125.7, 124.3, 123.1, 118.4, 115.62 (d, $J_{C,F}$ = 22 Hz), 109.9, 108.8, 101.8, 84.3, 83.9, 38.2; IR (ATR, cm^{-1}) 2971, 2916, 2850, 1651, 1590, 1525, 1504, 1454, 1345, 1076, 764, 715, 690; HRMS Calcd for ($C_{22}H_{16}FN_3$) $[M + H]^+$: 342.14010; Found: 342.14384.

3-Phenyl-5-(1-(3-(p-tolyl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)-1H-pyrazole ***(11f)***. A yellow colored viscous oil (97%, 0.49 mmol, 165 mg). R_f = 0.4 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.94 (bs, 1H), 7.80 (bd, J = 7.9 Hz, 2H), 7.45 (t, J = 7.2 Hz, 2H), 7.41-7.38 (m, 3H), 7.16 (bd, J = 7.7 Hz, 2H), 7.11 (bs, 1H), 6.87 (bd, J = 1.9 HZ, 1H 1H), 6.56 (dd, J = 3.5, 1.7 Hz, 1H), 6.34 (dd, J = 3.5, 2.6 Hz, 1H), 5.15 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 141.2, 138.8, 131.8, 131.2, 129.2, 128.9, 128.3, 125.8, 124.2, 123.2,

119.4, 110.1, 108.8, 101.9, 85.7, 83.5, 38.3, 21.5; IR (ATR, cm^{-1}) 3056, 2922, 1457, 1073; HRMS Calcd for ($C_{23}H_{19}N_3$) $[M + H]^+$: 338.16517; Found: 338.16333.

*3-Phenyl-5-(1-(3-phenylprop-2-yn-1-yl)-1H-pyrrol-2-yl)-1H-pyrazole (**11g**).* A light yellow viscous liquid (97%, 0.49 mmol, 157 mg). R_f = 0.4 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (bs, 1H), 7.59 (dd, J = 8.2, 1.1 Hz, 2H), 7.33 – 7.12 (m, 9H), 6.91 (dd, J = 2.8, 1.8 Hz, 1H), 6.65 (s, 1H), 6.35 (dd, J = 3.6, 1.8 Hz, 1H), 6.14 (dd, J = 3.6, 2.9 Hz, 1H), 4.98 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 140.0, 130.7, 130.1, 127.8, 127.5, 127.2, 124.6, 123.1, 122.1, 121.3, 108.9, 107.7, 100.8, 84.4, 83.0, 37.2; IR (ATR, cm^{-1}) 3105, 3050, 2918, 1605, 1456, 1284, 1178, 1073, 966, 908; HRMS Calcd for ($C_{22}H_{17}N_3$) $[M + H]^+$: 324.14952; Found: 324.15236.

*3-(4-Methoxyphenyl)-5-(1-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-1H-pyrrol-2-yl)-1H-pyrazole (**11h**).* A light yellow viscous liquid (88%, 0.44 mmol, 169 mg). R_f = 0.4 (ethyl acetate/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (bd, J = 8.7 Hz, 2H), 7.36 – 7.30 (m, 2H), 7.02 (dd, J = 2.6, 1.8 Hz, 1H), 6.92 (bd, J = 8.8 Hz, 2H), 6.80 (bd, J = 8.8 Hz, 2H), 6.67 (s, 1H), 6.44 (dd, J = 3.5, 1.8 Hz, 1H), 6.26 – 6.21 (m, 1H), 5.11 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.7, 146.1, 140.5, 133.3, 126.9, 124.3, 124.1, 123.1, 114.4, 114.3, 113.9, 109.8, 108.6, 101.3, 85.4, 82.8, 55.3, 55.3, 38.4; IR (ATR, cm^{-1}) 2962, 2928, 2834, 1606, 1506, 1245, 1173, 1028, 830; HRMS Calcd for ($C_{24}H_{21}N_3O_2$) $[M + H]^+$: 384.17065; Found: 384.17214.

*5-(1-Propyl-1H-pyrrol-2-yl)-1H-pyrazole (**12**).* A yellow viscous liquid. (85%, 0.43 mmol, 74 mg). R_f = 0.6 (ethyl acetate/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (bs, 1H), 7.55 (bd, J = 2.1 Hz, 1H), 6.77 – 6.75 (m, 1H), 6.39 (dd, J = 3.6, 1.8 Hz, 1H), 6.36 (d, J = 2.1 Hz, 1H), 6.19 (dd, J = 3.6, 2.9 Hz, 1H), 4.05 (t, J = .3 Hz, 2H), 1.71 (hextet, J = 7.3 Hz, 2H), 0.85 (t,

J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 133.8, 124.5, 123.1, 109.3, 107.7, 104.1, 49.5, 24.7, 11.2; IR (ATR, cm^{-1}) 3162, 2920, 2834, 1706, 1575, 1463, 1302, 1253, 1105, 1065, 1041, 764, 712; HRMS Calcd for ($C_{10}H_{13}N_3$) $[M + H]^+$: 176.11822; Found: 176.11776.

*Reaction of **11g** with different metal catalysts.* To a solution of pyrazole **11g** (0.5 mmol) in acetonitrile (10 mL) was added a solution of metal-catalysts (3% mol, see Table 3) in acetonitrile (1 mL) dropwise at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 3-24 h. The solvent was evaporated. The residue was purified by a short silica gel column eluting with ethyl acetate/hexane. The residue was analyzed by ^{1}H NMR spectroscopy.

General procedure for the synthesis of pyrazolo-pyrrolo-pyrazines and pyrazolo-pyrollo-diazepines via $AuCl_3$-catalyzed cyclization: To a solution of pyrazole **11** (0.4 mmol) in acetonitrile (10 mL) was added a solution of gold trichloride (2.5 mmol%, 3 mg) in acetonitrile (1 mL) dropwise at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 8-24 h. The solvent was evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate/hexane to give pyrazolo-pyrrolo-pyrazines and pyrazolo-pyrolo-diazepines **13-14**.

General procedure for the synthesis of pyrazolo-pyrrolo-pyrazines via NaH-promoted cyclization: To a solution of pyrazole **11** (0.4 mmol) in DMF (10 mL) was added sodium hydride (1.1 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 10-15 min. After complete conversion (monitored by TLC) water was added, and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined extracts were dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel eluting with ethyl acetate/hexane to give pyrazolo-pyrrolo-pyrazines **13**.

*5-Methylpyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**13a**).* A viscous oil (95%, 0.38 mmol, 65 mg). R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 2.0 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.66 – 6.62 (m, 1H), 6.60 (d, J = 2.0 Hz, 1H), 6.57 (dd, J = 3.7, 2.7 Hz, 1H), 2.53 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 133.0, 122.3, 121.8, 115.1, 111.8, 109.8, 101.8, 97.3, 14.7; IR (ATR, cm^{-1}) 3123, 3098, 2950, 2916, 2850, 1588, 1516, 1427, 1340, 1071, 1032, 921, 772, 722; HRMS Calcd for ($C_{10}H_9N_3$) $[M + H]^+$: 172.08692; Found: 172.08702.

*5-Methyl-2-phenylpyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**13b**).* A colorless viscous oil (91%, 0.36 mmol, 90 mg). R_f = 0.7 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.1, 1.2 Hz, 2H), 7.45 (bt, J = 7.6 Hz, 2H), 7.35 (bt, J = 7.1, 1H), 7.09 (bs, 1H), 6.92 (s, 1H), 6.68 (dd, J = 2.8, 1.0 Hz, 1H), 6.60 (dd, J = 3.8, 2.7 Hz, 1H), 2.60 (d, J = 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 134.3, 133.3, 128.7, 128.2, 126.2, 122.1, 115.2, 111.8, 109.8, 101.8, 94.4, 14.8; IR (ATR, cm^{-1}) 3101, 3059, 2959, 2919, 1593, 1502, 1454, 1422, 1369, 1335, 1074, 1023, 756, 687; HRMS Calcd for ($C_{16}H_{13}N_3$) $[M + H]^+$: 248.11822; Found: 248.11819.

*2-Butyl-5-methylpyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**13c**).* A viscous oil (87%, 0.35 mmol, 79 mg). R_f = 0.6 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, J = 2.4, 1.5 Hz, 1H), 7.03 (bs, 1H), 6.60 (bd, J = 3.7 Hz, 1H), 6.56 (dd, J = 3.7, 2.7 Hz, 1H), 6.43 (s, 1H), 2.78 (t, J = 7.8 Hz, 2H), 2.53 (d, J = 1.0 Hz, 3H), 1.72 (quintet, J = 7.7 Hz, 2H), 1.44 (hextet, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 133.6, 122.3, 121.8, 114.9, 111.6, 108.9, 101.3, 95.9, 32.0, 28.3, 22.6, 14.9, 13.9; IR (ATR, cm^{-1}) 3095, 2954, 2920, 2850, 1590, 1522, 1426, 1339, 1074, 763, 707, 689; HRMS Calcd for ($C_{14}H_{17}N_3$) $[M + H]^+$: 228.14952; Found: 228.15045.

*5-(3-Nitrobenzyl)-2-phenylpyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**13d**).* A yellow colored solid (93%, 0.37 mmol, 136 mg), mp 187-189 °C. R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 1.7 Hz, 1H), 8.04 (dd, J = 8.2, 1.3 Hz, 1H), 7.85 (bd, J = 7.0 Hz, 2H), 7.73 (bd, J = 7.7 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 2H), 7.28 (tt, J = 7.4, 1.2 Hz, 1H), 7.03 (dd, J = 2.6, 1.3 Hz, 1H), 6.96 (bs, 1H), 6.83 (s, 1H), 6.62 (bd, J = 3.6 Hz, 1H), 6.55 (dd, J = 3.7, 2.8 Hz, 1H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 148.4, 139.3, 135.6, 134.3, 133.0, 129.4, 128.7, 128.3, 126.1, 124.5, 124.0, 122.1, 122.0, 115.9, 112.4, 110.9, 102.3, 94.6, 34.4; IR (ATR, cm^{-1}) 3095, 3064, 2967, 2921, 2857, 1520, 1505, 1339, 1075; HRMS Calcd for ($C_{22}H_{16}N_4O_2$) $[M + H]^+$: 369.1346; Found: 369.13842.

*5-(4-Fluorobenzyl)-2-phenylpyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**13e**).* A yellow colored viscous oil (85%, 0.34 mmol, 116 mg). R_f = 0.7 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.34-7.28 (m, 3H), 6.98-6.96 (m, 3H), 6.85 (s, 1H), 6.70 (s, 1H), 6.61 (bd, J = 3.6 Hz, 1H), 6.52 (dd, J = 3.6, 2.8 Hz, 1H), 4.27 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.97 (d, $J_{C,F}$ = 244 Hz), 152.4, 134.2, 133.2, 132.3, 131.17 (d, $J_{C,F}$ = 8 Hz), 128.7, 128.2, 126.1, 125.7, 122.0, 115.64 (d, $J_{C,F}$ = 8 Hz), 115.4, 112.1, 110.7, 102.0, 94.5, 33.8; IR (ATR, cm^{-1}) 2988, 2967, 2918, 2899, 1507, 1455, 1219, 1068; HRMS Calcd for ($C_{22}H_{16}FN_3$) $[M + H]^+$: 342.1401; Found: 342.14329.

*5-(4-Methylbenzyl)-2-phenylpyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**13f**).* A colorless solid (82%, 0.33 mmol, 111 mg), mp 146-148 °C. R_f = 0.6 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 7.1, 1.3 Hz, 2H), 7.45 (bt, J = 7.5, 2H), 7.36 (bt, J = 7.5, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.18 (bd, J = 7.8 Hz, 2H), 7.01 (dd, J = 2.8, 1.3 Hz, 1H), 6.93 (s, 1H), 6.73 (bs, 1H), 6.67 (bd, J = 3.7 Hz, 1H), 6.57 (dd, J = 3.7, 2.8 Hz, 1H), 4.34 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 136.6, 134.2, 133.4, 133.3, 129.7, 129.4, 128.7, 128.1, 126.3,

126.2, 122.0, 115.6, 112.0, 110.7, 101.8, 94.4, 34.1, 21.1; IR (ATR, cm^{-1}) 2988, 2964, 2920, 2896, 1588, 1454, 1338, 1076; HRMS Calcd for ($C_{23}H_{19}N_3$) $[M + H]^+$: 338.16517; Found: 338.16418.

*5-Benzyl-2-phenylpyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**13g**).* A yellow colored solid (90%, 0.36 mmol, 116 mg), mp 127-129 °C. R_f = 0.7 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.4 Hz, 2H), 7.49-7.21 (m, 8H), 6.93 (dd, J = 2.7, 1.4 Hz, 1H), 6.85 (s, 1H), 6.65 (s, 1H), 6.60 (bd, J = 3.5 Hz, 1H), 6.50 (dd, J = 3.5, 2.7 Hz, 1H), 4.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 136.6, 134.2, 133.3, 129.8, 128.7, 128.6, 128.2, 127.0, 126.2, 125.9, 122.0, 115.7, 112.0, 110.8, 101.8, 94.5, 34.5; IR (ATR, cm^{-1}) 2970, 2918, 1455, 1362, 1071; HRMS Calcd for ($C_{22}H_{17}N_3$) $[M + H]^+$: 324.14952; Found: 324.15291.

*5-(4-Methoxybenzyl)-2-(4-methoxyphenyl)pyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**13h**).* A yellow colored viscous oil (74%, 0.29 mmol, 113 mg). R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (bd, J = 8.8 Hz, 2H), 7.27 (bd, J = 8.6 Hz, 2H), 6.95 (dd, J = 2.6, 1.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.79 (s, 1H), 6.63 (s, 1H), 6.59 (bd, J = 3.7 Hz, 1H), 6.50 (dd, J = 3.7, 2.6 Hz, 1H), 4.25 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 158.7, 152.2, 134.2, 130.8, 128.5, 127.4, 126.4, 126.1, 122.0, 115.5, 114.1, 114.1, 111.9, 110.4, 101.6, 93.9, 55.3, 55.3, 33.6; IR (ATR, cm^{-1}) 3055, 2922, 2814, 1357, 1073; HRMS Calcd for ($C_{24}H_{21}N_3O_2$) $[M + H]^+$: 384.17065; Found: 384.17448.

*5-(3-Nitrophenyl)-2-phenyl-7H-pyrazolo[1,5-a]pyrrolo[2,1-c][1,4]diazepine (**14d**).* A yellow colored solid (83%, 0.33 mmol, 122 mg), mp 97-98 °C. R_f = 0.4 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, J = 2.2, 1.7 Hz, 1H), 8.23 (ddd, J = 8.1, 2.2, 1.0 Hz, 1H), 7.76 (dd, J = 8.2, 1.6 Hz, 2H), 7.61 (bd, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.38

– 7.32 (m, 3H), 6.87 (s, 1H), 6.79 (dd, J = 2.6, 1.6 Hz, 1H), 6.63 (dd, J = 3.7, 1.6 Hz, 1H), 6.27 (dd, J = 3.7, 2.6 Hz, 1H), 6.09 (t, J = 7.4 Hz, 1H), 4.65 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 148.2, 143.4, 138.4, 134.5, 132.4, 128.9, 128.6, 128.5, 126.0, 123.8, 123.3, 122.9, 122.3, 114.6, 110.1, 108.9, 102.7, 43.6; IR (ATR, cm^{-1}) 2968, 2919, 2850, 1648, 1593, 1526, 1345, 1078, 1028, 803, 765, 690; HRMS Calcd for ($C_{22}H_{16}N_4O_2$) $[M + H]^+$: 369.13460; Found: 369.13738.

5-(4-Fluorophenyl)-2-phenyl-7H-pyrazolo[1,5-a]pyrrolo[2,1-c][1,4]diazepine ***(14e)***. A light yellow viscous liquid (90%, 0.36 mmol, 123 mg). R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.3, 1.2 Hz, 2H), 7.37 (bt, J = 7.3 Hz, 2H), 7.32 – 7.28 (m, 3H), 7.01 (t, J = 8.7 Hz, 2H), 6.83 (s, 1H), 6.76 – 6.72 (m, 1H), 6.59 (dd, J = 3.7, 1.6 Hz, 1H), 6.23 (dd, J = 3.7, 2.7 Hz, 1H), 5.91 (t, J = 7.5 Hz, 1H), 4.55 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.22 (d, $J_{C,F}$ = 248 Hz), 152.1, 144.5, 140.7, 132.7 (d, $J_{C,F}$ = 11 Hz), 130.25 (d, $J_{C,F}$ = 9 Hz), 128.6, 128.3, 126.0, 123.1, 122.0, 115.2, 114.9, 112.8, 109.7, 108.7, 102.4, 43.6; IR (ATR, cm^{-1}) 3066, 2919, 2846, 1647, 1594, 1506, 1367, 1230, 1157, 1078, 906, 765, 725, 693; HRMS Calcd for ($C_{22}H_{17}N_3F$) $[M + H]^+$: 342.14010; Found: 342.14436.

2-Phenyl-5-(p-tolyl)-7H-pyrazolo[1,5-a]pyrrolo[2,1-c][1,4]diazepine ***(14f)***. A colorless viscous oil (95%, 0.38 mmol, 128 mg). R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.0, 1.1 Hz, 2H), 7.46 (bt, J = 7.0 Hz, 2H), 7.39 (dd, J = 7.0 Hz, 1H), 7.30 (bd, J = 7.9 Hz, 2H), 7.21 (bd, J = 7.9 Hz, 2H), 6.93 (bs, 1H), 6.80 (dd, J = 3.6, 2.1 Hz, 1H), 6.69 (dd, J = 3.6, 1.8 Hz, 1H), 6.32 (dd, J = 3.6, 1.8 Hz, 1H), 5.99 (t, J = 7.5 Hz, 1H), 4.59 (d, J = 7.5 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 145.4, 140.7, 139.0, 134.0, 132.9, 128.8, 128.6, 128.3, 128.2, 126.1, 123.3, 122.0, 112.5, 109.5, 108.6, 102.3, 43.7, 21.4; IR (ATR,

cm^{-1}) 2969, 2918, 2851, 1365, 1054; HRMS Calcd for ($C_{23}H_{19}N_3$) $[M + H]^+$: 338.16517; Found: 338.16526.

*2,5-Diphenyl-7H-pyrazolo[1,5-a]pyrrolo[2,1-c][1,4]diazepine (**14g**)*. A yellow colored solid (95%, 0.38 mmol, 123 mg), mp = 85-86 °C. R_f = 0.5 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.3, 1.2 Hz, 2H), 7.34 – 7.19 (m, 8H), 6.75 (s, 1H), 6.66 (dd, J = 2.5, 1.8 Hz, 1H), 6.51 (dd, J = 3.7, 1.8 Hz, 1H), 6.15 (dd, J = 3.6, 2.5 Hz, 1H), 5.88 (t, J = 7.5 Hz, 1H), 4.48 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 145.5, 140.7, 136.7, 132.8, 129.0, 128.6, 128.4, 128.2, 128.0, 126.1, 123.2, 121.9, 113.2, 109.6, 108.6, 102.3, 43.7; IR (ATR, cm^{-1}) 3056, 2919, 2850, 1642, 1593, 1496, 1448, 1366, 1074, 1026, 762, 691; HRMS Calcd for ($C_{22}H_{17}N_3$) $[M + H]^+$: 324.14952; Found: 324.15137.

*2,5-Bis(4-methoxyphenyl)-7H-pyrazolo[1,5-a]pyrrolo[2,1-c][1,4]diazepine (**14h**)*. A yellow colored solid (96%, 0.39 mmol, 115 mg), mp 80-81 °C. R_f = 0.4 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (bd, J = 8.9 Hz, 2H), 7.19 (bd, J = 8.8 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.83 (s, 1H), 6.69 – 6.64 (m, 2H), 6.50 (dd, J = 3.7, 1.6 Hz, 1H), 6.15 (dd, J = 3.7, 2.6 Hz, 1H), 5.80 (t, J = 7.5 Hz, 1H), 4.47 (d, J = 7.5 Hz, 2H), 3.744 (s, 3H), 3.741 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.5, 150.4, 143.8, 139.3, 128.5, 128.1, 126.1, 124.4, 122.1, 120.5, 112.7, 112.2, 110.1, 108.1, 107.3, 100.6, 54.1 (2C), 42.5; IR (ATR, cm^{-1}) 2956, 2919, 2846, 1642, 1609, 1505, 1245, 1174, 1029, 865, 719; HRMS Calcd for ($C_{24}H_{21}N_3O_2$) $[M + H]^+$: 384.17065; Found: 384.17457.

(*Z)-2-phenyl-5-(pyridin-2-ylmethylene)-5,6-dihydropyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine* (**21**): The compound has been synthesized by the reaction of **10f** with hydrazine as described described above. A yellow colored solid (92%, 0.37 mmol, 119 mg), mp = 135-137 °C. R_f = 0.6 (ethyl acetate/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.8 Hz, 1H), 7.93 (d, J =

7.3 Hz, 2H), 7.61 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.45 – 7.41 (t, *J* = 7.4 Hz, 3H), 7.34 (d, *J* = 7.0 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H) 7.07 (dd, *J* = 7.3, 4.8 Hz, 1H), 6.83 (bs, 1H), 6.68 (s, 1H), 6.47 (bd, *J* = 2.5 Hz, 1H), 6.27 (dd, *J* = 3.7, 2.5 Hz, 1H), 5.86 (d, *J* = 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 153.8, 149.0, 136.3, 135.3, 132.8, 132.6, 128.7, 128.5, 126.1, 125.5, 121.7, 120.9, 120.7, 111.9, 110.2, 105.6, 97.2, 45.6; IR (ATR, cm^{-1}) 3104, 3062, 3038, 2995, 2916, 2850, 1967, 1906, 1634, 1620, 1584, 1404, 1356, 1300, 1146, 1070, 1023, 951, 763, 715; HRMS Calcd for ($C_{21}H_{16}N_4$) $[M + H]^+$: 325.14477; Found: 325.14395.

*2-Phenyl-5-(pyridin-2-ylmethyl)pyrazolo[1,5-a]pyrrolo[2,1-c]pyrazine (**22**):* To a solution of **21** (119 mg, 0.37 mmol) in methylene chloride (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (100 μL, 0.7 mmol). The reaction mixture was stirred at room temperature for 0.5 h. After completion of the reaction (controlled by TLC), water (5 mL) was added, and the solution was extracted with methylene chloride. The combined organic extracts were dried over $MgSO_4$. The solvent was evaporated to give crude product, which was purified by column chromatography over silica gel eluting with EtOAc/hexane (1:2) to **22** as a yellow colored solid (97%, 0.36 mmol, 117 mg), mp 147-149 °C. R_f = 0.3 (ethyl acetate/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.62 (dt, *J* = 7.6, 1.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.07 (dd, *J* = 2.7, 1.4 Hz, 1H), 6.89 (s, 1H), 6.66 (bd, *J* = 3.7 Hz, 1H), 6.58 (dd, *J* = 3.7, 2.7 Hz, 1H), 4.51 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 152.2, 149.4, 136.7, 134.3, 133.3, 128.7, 128.1, 126.1, 124.4, 123.7, 122.1, 121.9, 115.8, 112.1, 111.3, 101.9, 94.4, 37.1; IR (ATR, cm^{-1}) 3107, 2970, 2901, 1583, 1461, 1282, 1073, 960, 761, 716, 692; HRMS Calcd for ($C_{21}H_{16}N_4$) $[M + H]^+$: 325.14477; Found: 325.14224.

Associated Content

Supporting Information: Spectroscopic data (1D and 2D NMR spectra) of the products and the X-ray crystal structure of **22**. This material is available free of charge via the Internet at http://pubsacs.org.

Author Information

Corresponding Author

*E-mail: mbalci@metu.edu.tr

Notes

The authors declare no competing financial interest.

Acknowledgement

Financial support from the Scientific and Technological Research Council of Turkey (TUBITAK, Grant No. TBAG-112 T360), the Turkish Academy of Sciences (TUBA), and Middle East Technical University (METU) is gratefully acknowledged. Furthermore, we are grateful to Prof. Ertan Şahin (Atatürk University, Erzurum/Turkey) for X-ray analysis.

References

(1) (a) Kumari, S.; Paliwal, S.; Chauhan, R. *Synthetic Commun.* **2014**, *44*, 1521-1578. (b) Alex, J. M.; Kumar, R. *J. Enzym Inhib. Med. Ch.* **2014**, *29*, 427-442. (c) Kumar, V.; Kaur, K. T; Gupta, G. K.; Sharma, A. K. *Eur. J. Med. Chem.* **2013**, *69*, 735-753. (d) Li, J. J., Edit. by Li, J. J. Heterocyclic Chemistry in Drug Discovery **2013**, 198-229, Wiley. (e) Panda, N.; Jena, A. K. *J.*

Org. Chem. **2012**, *77*, 9401-9406. (f) Deng, X.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2412-2415. (g) Deng, X.; Mani, N. S. *Org. Lett.,* **2008**, *10*, 1307-1310.

(2) (a) Klatt, T.; Markiewicz, J. T.; Saemann, C.; Knochel, P. *J. Org. Chem.* **2014**, *79*, 4253-4269. (b) Nikishkin, N. I.; Huskens, J.; Verboom, W. *Org. Biomol. Chem.* **2013**, *11*, 3583-3602. (c) Yet, L. From Progress in Heterocyclic Chemistry **2012**, 24, 393-420, Pergamon. (d) He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla J. C. *Org. Lett.,* **2011**, *13*, 4490-4493. (e) Manlove, A.; Groziak, M. P. Progress in Heterocyclic Chemistry, **2009**, *21*, 375-414.

(3) Likhosherstov, A. M.; Filippova, O. V.; Peresada, V. P.; Kryzhanovskii, S.A.; Vititnova,M. B.;Kaverina, N. V.;Reznikov, K. M. *Pharm. Chem. J.* **2003**, *37*, 6-9.

(4) Seredenin, S. B.; Voronina, T. A.; Beshimov, A.; Peresada, V. P.; Likhosherstov, A. M. RU 2099055, **1997**.

(5) Seredenin, S. B.; Voronina, T.A.; Likhosherstov,A.M.; Peresada, V. P.; Molodavkin, G. M.; Halikas, J. A. US 5378846, **1995**, 10.

(6) Peresada,V. P.;Medvedev,O. S.;Likhosherstov, A. M.; Skoldinov, A. P. *Khim.-Farm. Zh.* **1987**, *21*, 1054-1059.

(7) Negoro, T.; Murata, M.; Ueda, S.; Fujitani, B.; Ono, Y.; Kuromiya, A.; Komiya, M.; Suzuki, K.; Matsumoto, J.-i. *J. Med. Chem.* **1998**, *41*, 4118-4129.

(8) (a) French, J. M.; Diver, S. T. *J. Org. Chem.* **2014**, *79,* 5569-5585. (b) Li, Y.; Xu, M.-H. *Org. Lett.* **2014**, *16,* 2712-2715. (c) Ghosh, P.; Saha, P.; Bondalapati, S.; Indukuri, K.; Saikia, A. K. *J. Org. Chem.* **2014**, *79,* 4119-4124. (d) Rao, S. S.; Rambabu, D.; Layek, M.; Kumar, K. L.; Rao, M. V. B.; Haldar, D.; Pal, M. *Lett. Drug Des. Discov.* **2104**, *11,* 199-206. (e) Alcaide, B.; Almendros, P. *Accounts Chem. Res.* **2014,** *47,* 939-952. (f) Pawar, L.; Pigge, F. C. *Tetrahedron*

Lett. **2013**, *54,* 6067-6070. (g) Gronnier, C.; Boissonnat, G.; Gagosz, F. Org. *Lett.* **2013**, 15, 4234-4237.

(9) (a) Shi, Y.; Gevorgyan, V. *Org. Lett*. **2013**, *15*, 5394-5396. (b) Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.* **2011**, *13*, 3746-3749. (c) Kovacs, G.; Lledos, A.; Ujaque, G. *Angew. Chem. Int. Ed.*. **2011**, *50,* 11147-11151. (d) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111,* 6513-6556. (e) Leyva-Perez, A.; Cabrero-Antonino, J. R.; Cantin, A.; Corma, A. *J. Org. Chem.* **2010**, *75,* 7769-7780. (f) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel P. *Tetrahedron.* **2003**, *59*, 1571-1587.

(10) (a) Minguez, J. M.; Castellote, M. I.; Vaquero, J. J.; Garcıa-Navio, J. L.; Alvarez-Builla, J.; Castano, O.; Andres, J. L. *J. Org. Chem.* **1996**,*61,* 4655-4655. (b) Harrington, R. W.; Stanforth, S. P. *Tetrahedron Lett.* **2012**, *53,* 2111-2113.

(11) (a) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *132,* 5151-5169. (b) Rudolph, M. In *Modern Gold Catalyzed Synthesis;* Hashmi, A. S. K.; Toste, F. D. Eds.; Wiley: Weinheim, Germany, **2012**, 331-362. (c) Cgeon, C. H.; Kanno, O.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133,* 13248-13251. (d) Barluenga, J.; Sigüerio, R.; Vicente, R.; Ballesteros, A.; Tomas, M.; Rodriguez, M. A. *Angew. Chem., Int. Ed.* **2012**, *51,* 10377-10381. (e) Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem., Int. Ed.* **2010**, *49,* 2542-2546. (f) Hashmi, A. S. K. *Chem. Rev.* **2007,** *107,* 3180-3211. (g) Alcaide, B.; Almendros, P.; Quiros, M. T.; Fernandez, I. *Beilstein J. Org. Chem.* **2013**, *9,* 818-826.

(12) Menges, N.; Sari, O.; Abdullayev, Y.; Erdem, S. S.; Balci, M. *J. Org. Chem.* **2013**, *78*, 5184-5195.

(13) (a) Chinchilla, R.; Najera. C. *Chem. Rev.* **2007**, *107,* 874-922. (b) Douchet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed.* **2007**, *46,* 834-871. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N.

Tetrahedron Lett. **1975**, *16.* 4467-4470. (d) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6,* 347-4289. (e) Caporale, A.; Tartaggia, S.; Castellin, A.; Lucchi, O. D. *Beilstein J. Org. Chem.* **2014**, *10,* 384-393.

(14) Murray, W.; Watcher, M. *J. Heterocycl. Chem.* **1989**, *26,* 1389-1392.

(15) Moure, Ch.; Delange R. *Bull. Soc. Chim. Fr.* **1901**, *25,* 302-313.

(16) Zora, M.; Kivrak, A.; Yazici C. *J. Org. Chem.* **2011**, *76,* 6726-6742.

(17) Menges, N.; Balci, M. *Synlett,* **2014**, *25*, 671-676.

(18) For isomeric pyrazolo-pyrrolo-pyrazines see: (a) Farghaly, A.-R.; Hussein El-Kashef, H. *J. Heterocyclic Chem*. **2011**, *48,* 678-683. (b) Farghaly, A.-R.; Hussein El-Kashef, H. *Monatsh. Chem.* **2005**, *136*, 217-227.

(19) (a) Hansmann, M. M.; Tsupova, S.; Rudolph, M.; Rominger, F. Hashmi, A. S. K. *Chem. A Eur. J.* **2014**, *20,* 2215-2223. (b) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130,* 5636-5637. (c) Manzo, A. M.; Perboni, A. D.; Broggini, G.; Rigamonti, M. *Tetrahedron Lett.* **2009**, *50,* 4696-4699.

(19) Brooner, R. E.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2013**, *52,* 11714-11724. (b) Alcaide, B.; Almendros, P. *Beilstein J. Org. Chem.* **2011**, *7,* 622-630.

(20) For isomeric pyrazolo-pyrrolo-diazepine derivatives see : (a) Vega, S.; Gil, M. S.; Darias, V.; Mateo, C. C. S.; Expósito, M. A.; Oset-Gasque, M. J.; Parramón, M.; González, M. P. *Eur. J. Med. Chem.* **1994,** *29,* 233-239. (b) Massa, S.; Stefancich, G.; Artico, M.; Corelli, F. *J. Heterocyclic Chem.* **1984**, *21*, 1877-1880.

(21) We assume that the configuration is (*E*). For similar stereochemistry see: Patil, N. T.; Lutete, L. M.; Nishina, N.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47,* 4749-4751.