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Novel intramolecular cyclization of *N*-alkynyl heterocycles containing proximate nucleophiles

Giorgio Abbiati,[a] Antonio Arcadi,[b] Egle Beccalli[a] and Elisabetta Rossi[a,*]

[a]*Istituto di Chimica Organica 'Alessandro Marchesini', Facoltà di Farmacia, Università degli Studi di Milano, Via Venezian, 21, 20133 Milano, Italy*

[b]*Dipartimento di Chimica, Ingegneria Chimica e Materiali, Facoltà di Scienze, Università de L'Aquila, Via Vetoio, Coppito due, 67100 L'Aquila, Italy*

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Abstract—Intramolecular cyclization of 2-acyl-1-propargyl-1*H*-indoles in the presence of ammonia provides an easy entry to pyrazino[1,2-*a*]indole nucleus.

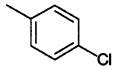
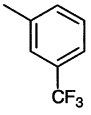
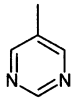
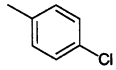
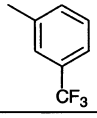
In connection with our ongoing interest in developing new synthetic strategies for the construction of heterocycles from alkynes,[1] we have recently focused our attention on the synthesis of nitrogen containing rings by sequential addition annulation reactions of γ-ketoalkynes with benzylamine or ammonia. In particular, 5-*exo*-*dig* cyclization of 4-pentynones[2] and 2-propynyl-1,3-dicarbonyl[3] compounds gave polysubstituted and fused pyrrole derivatives, while the presence of γ-ketoalkyne moiety in an aromatic framework is responsible for the 6-*endo*-*dig* cyclization of 5-acetyl-4-alkynylthiazoles[4] and 2-acyl-3-alkynylindoles[5] to pyrido[3,4-*c*]thiazoles and pyrido[3,4-*b*]indoles, respectively.

In this work we focused our attention on the synthesis of 2-acyl-1-propargyl-1*H*-indoles, which could represent useful building blocks for the synthesis of pyrazino[1,2-*a*]indoles through intramolecular 6-*exo*-*dig* cyclization in the presence of ammonia.

Scheme 1.

A great deal of interest exists in the synthesis of polycyclic indoles and in the study of their biological

Table 1. 1-Alkynyl derivatives **1c–h** prepared

	R	Ar	X	Yield[a] (%)	Mp °C
1c	CH_3		I	72	107-109
1d	CH_3		I	82	67
1e	CH_3		Br	83	148
1f	H		I	71	76
1g	H		I	88	78
1h	H		I	88	91-93

[a]The synthesis of 1-alkynyl-1*H*-indoles **1c-h** was carried out in DMF at 60°C, using the following molar ratios: alkyne/aryl halide/K_2CO_3/CuI/$Pd(PPh_3)_4$ = 1:1:5:0.04:0.02.

Keywords: indoles; alkynes; pyrazino[1,2-*a*]indoles; palladium; annulation reactions.

* Corresponding author. Tel.: +39-02-50314474; fax: +39-02-50314476; e-mail: elisabetta.rossi@unimi.it

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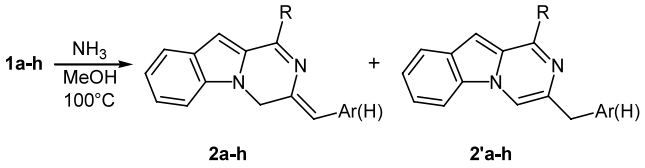
activities[6] and some studies dedicated to the pyrazino[1,2-*a*]indole nucleus have appeared in the literature.[7]

Intramolecular cyclizations involving 2-substituted-1-alkynyl pyrrole or indole derivatives have been described in the synthesis of indolophenanthridine and isoindoloindole derivatives,[8] pyrrolizines,[9] pyrrolophenanthridines,[10] 4a-aza-cyclopentafluorenes,[11] pyridopyrrolizines and 10-aza-indenoindoles.[12] Nevertheless, intramolecular cyclizations of 1-alkynyl indole derivatives or more generally of *N*-alkynyl substituted heterocycles with proximate nitrogen nucleophiles have not yet been described.

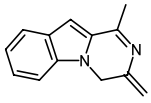
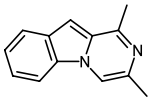
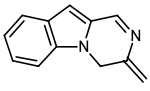
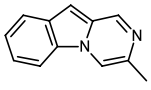
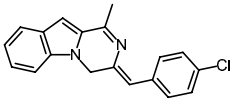
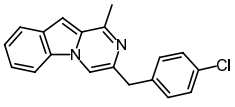
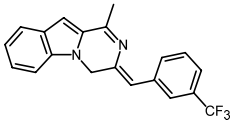
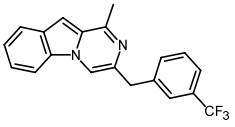
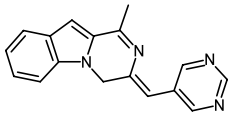
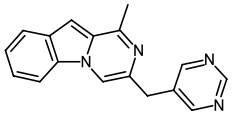
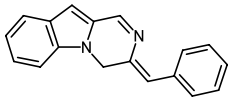
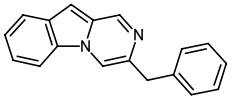
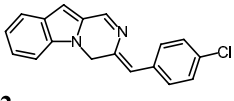
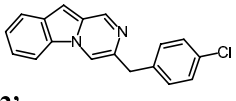
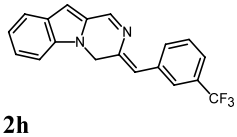
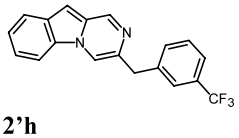
The 2-acyl-1-propargyl-1*H*-indole **1a** and 1-propargyl-1*H*-indole-2-carbaldehyde **1b**[12] were synthesized by a standard procedure,[13] starting from readily accessible 2-acyl-1*H*-indole[14] and 1*H*-indole-2-carbaldehyde,[15] respectively. The 1-propargyl-1*H*-indoles **1a**–**b** undergo palladium-catalyzed coupling with aryl halides[16] to afford the corresponding 2-acyl-1-alkynyl-1*H*-indoles **1c**–**e** and 1-alkynyl-1*H*-indole-2-carbaldehydes **1f**–**h** (Scheme 1, Table 1).

The subsequent treatment of **1** with 2 M ammonia in methanol leads to the formation of a mixture of isomeric 3,4-dihydro-pyrazino[1,2-*a*]indoles **2a**–**h** and pyrazino[1,2-*a*]indoles **2′a**–**h** (Scheme 2 and Table 2).[17]



Scheme 2.

Table 2. Pyrazino[1,2-*a*]indoles **2a**–**h** and **2′a**–**h** prepared

Entry	Reaction time	2	Yield %	Mp °C	2’	Yield %	Mp °C
1	50	 **2a**	-	-	 **2’a**	80	82
2	4	 **2b**	-	-	 **2’b**	73	173
3	200	 **2c**	31	132	 **2’c**	58	144
4	160	 **2d**	12	Yellow oil	 **2’d**	76	103
5	100	 **2e**	-	-	 **2’e**	69	156-157
6	3.5	 **2f**	35	121	 **2’f**	12	89
7	3	 **2g**	58	151	 **2’g**	30	124
8	3	 **2h**	46	Yellow oil	 **2’h**	26	114

The reaction times vary from 3–4 h for the carbaldehyde derivatives, to 50–200 h for the 2-acyl derivatives. The stereochemistry around the exocyclic double bond was assigned on the basis of NOESY experiments which shown positive NOE interaction between the exocyclic olefinic proton and the cyclic methylene protons.

The reaction mechanism probably involves the formation of an imine that undergoes a stereoselective 6-*exo*-*dig* cyclization to 3,4-dihydropyrazinoindoles **2a**–**h** followed by partial isomerization to give pyrazinoindoles **2′a**–**h**. The ratio between compounds **2** and **2′** is switched towards the formation of the fully conjugated rings in the experiments performed with terminal alkynes **1a**,**b** or with 2-acyl derivatives **1c**–**e** whereas dihydro derivatives are the main products when the reactions are performed with indole-2-carbaldehydes **1f**–**h**. This experimental evidence could be related to the great stability of compounds **2′a**,**b** with respect to **2a**,**b** and to the different reaction times required in the reaction performed with 2-acyl derivatives with respect to indole-2-carbaldehydes.

The present study demonstrates once again the efficiency of annulation reactions involving alkynes with neighboring nucleophiles and clearly suggests that such cyclizations could be effective also for *N*-alkynyl derivatives. Current efforts are now directed to the extension of this methodology to different substituted 1-alkynyl-2-acyl-1*H*-indoles, to the decrease of reaction times and to the selective synthesis of both pyrazinoindole isomers. For example, salts or complexes of transition metals successfully catalyze the intramolecular addition of nitrogen nucleophiles to alkynes[18] and could be used to speed up our annulation reactions and to direct the synthesis toward the more stabilized pyrazinoindole isomer.

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17. Typical procedure for compounds **2c** and **2′c**. A solution of 1-[3-(4-chloro-phenyl)-prop-2-ynyl]-2-acetyl-1*H*-indole **1c** (100 mg, 0.325 mmol) in dry ammonia and methanol (NH_3/MeOH 2 M solution, 3 mL) was heated at 100°C in a sealed tube for 200 h. The solvent was then evaporated under reduced pressure. The residue, purified by flash chromatography (petroleum ether/ethyl acetate, 98:2), yields progressively 3,4-dihydropyrazino[1,2-*a*]indole **2c** and pyrazino[1,2-*a*]indole **2′c**. **2c**: yellow solid. Mp: 132°C; ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 4.85 (d, 2H, $J=1.6$ Hz), 6.16 (t, 1H, $J=1.6$ Hz), 6.89 (s, 1H), 7.14–7.38 (m, 5H), 7.76 (d, 1H, $J=8.1$), 7.90 (m, 2H); ^{13}C NMR (APT) δ ($CDCl_3$) 22.6 (CH_3), 44.2 (CH_2), 103.9, 109.6, 121.1, 122.2, 122.9, 124.9, 128.6, 131.9 (Csp_2H), 127.9, 129.3, 133.1, 134.9, 137.6, 138.5, 157.2 (quat. Csp_2); IR (KBr) ν 1549, 1521, 1384, 1263, 868, 839, 798, 748, 734 cm^{-1}. Anal. calcd for $C_{19}H_{15}ClN_2$: C, 74.38; H, 4.93; N, 9.13. Found: C, 74.32; H, 4.94; N, 9.16. **2′c**: pale yellow solid. Mp: 144°C; ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H),

4.08 (s, 2H), 6.96 (s, 1H), 7.28–7.41 (m, 6H), 7.76 (s, 1H), 7.80–7.91 (m, 2H); ^{13}C NMR (DEPT) δ ($CDCl_3$) 22.3 (CH_3), 40.5 (CH_2), 94.6, 111.0, 112.8, 122.1, 122.2, 123.5, 128.8, 130.6 (Csp_2H), 128.4, 129.4, 129.8, 132.4, 135.0, 137.8, 154.9 (quat. Csp_2); IR (KBr) ν 1491, 1456, 1404, 1092, 796, 773, 739 cm^{-1}. Anal. calcd for $C_{19}H_{15}ClN_2$: C, 74.38; H, 4.93; N, 9.13. Found: C, 74.36; H, 4.90; N, 9.18.

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