CYCLIZATION REACTIONS OF ARYLHYDRAZONE ADDUCTS - SYNTHESIS OF 1-ARYL-1H-1,2,4-TRIAZOLO[4,3-b]INDAZOLES

Giuseppe Cusmano, Gabriella Macaluso, Michelangelo Gruttadauria, and Silvestre Buscemi

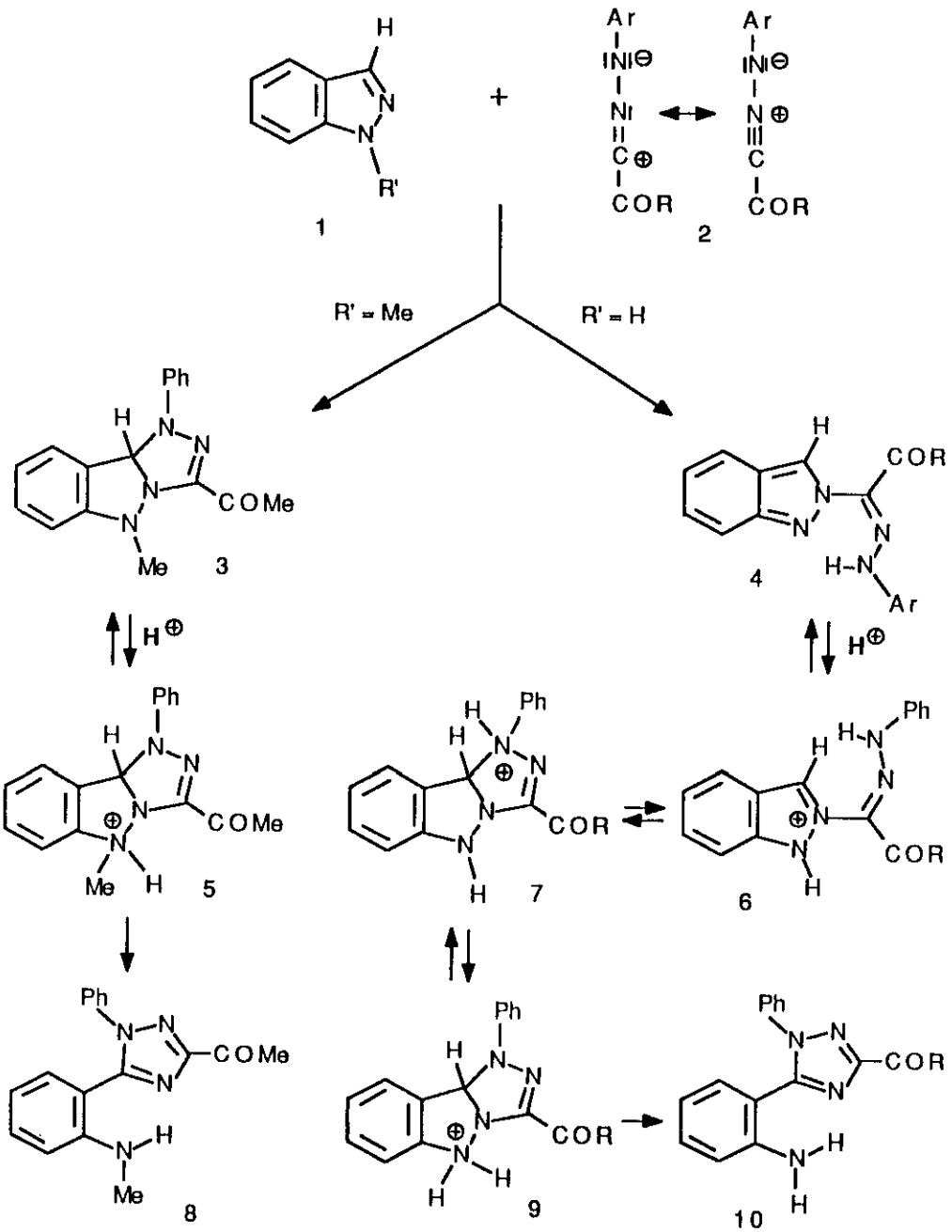
Dipartimento di Chimica Organica, Università di Palermo, Via Archirafi, 20, 90123, Palermo, Italy

Abstract ——— The 1,3-addition reaction of nitrilimines to 3-indazolinone **11** and the acid assisted 6 π heteroelectrocyclic reaction of hydrazone adducts **13** have been investigated. Synthesis of the 1,3-substituted 1H-1,2,4-triazolo[4,3-b]-indazole system **17** via cyclization of **13** is described.

The 1,3-dipolar cycloaddition and 1,3-addition reaction of 1,3-dipoles are valuable methods for the synthesis of heterocyclic systems.[1]

In previous papers on this topic we reported the results of studies on the dipolarophilic reactivity of the 1-methylindazole[2] and of the unsubstituted indazole[3,4] towards nitrilimines **2**. The formation of the cycloadduct **3** by 1,3-dipolar cycloaddition to 1-methylindazole (R'=Me)[2] and the regioselectivity of the 1,3-addition reaction of a variety of nitrilimines **2** with the unsubstituted indazole (R'=H)[3,4] have shown that the indazole system can be a convenient starting substrate for the annelation of the 1,2,4-triazole system. In fact, the hydrazone adducts **4** undergo an acid catalyzed rearrangement,[3] which implies an initial 6π heteroelectrocyclic reaction[5] to the intermediate dihydro-1,2,4-triazolo[4,3-b]indazoles **7**, followed by a subsequent ring opening to **10** through the N-N bond cleavage in the protonated structure **9**. Moreover, a similar ring opening, in the protonated cycloadduct **5**, gave the 1,2,4-triazole derivative **8**.[2]

In connection with our interest in developing new synthetic methods for the preparation of polycondensed heterocyclic compounds through 1,3-addition and rearrangement reactions,[3,6,7] we have investigated the reaction of 3-indazolinone **11** with nitrilimines **2a-f**.



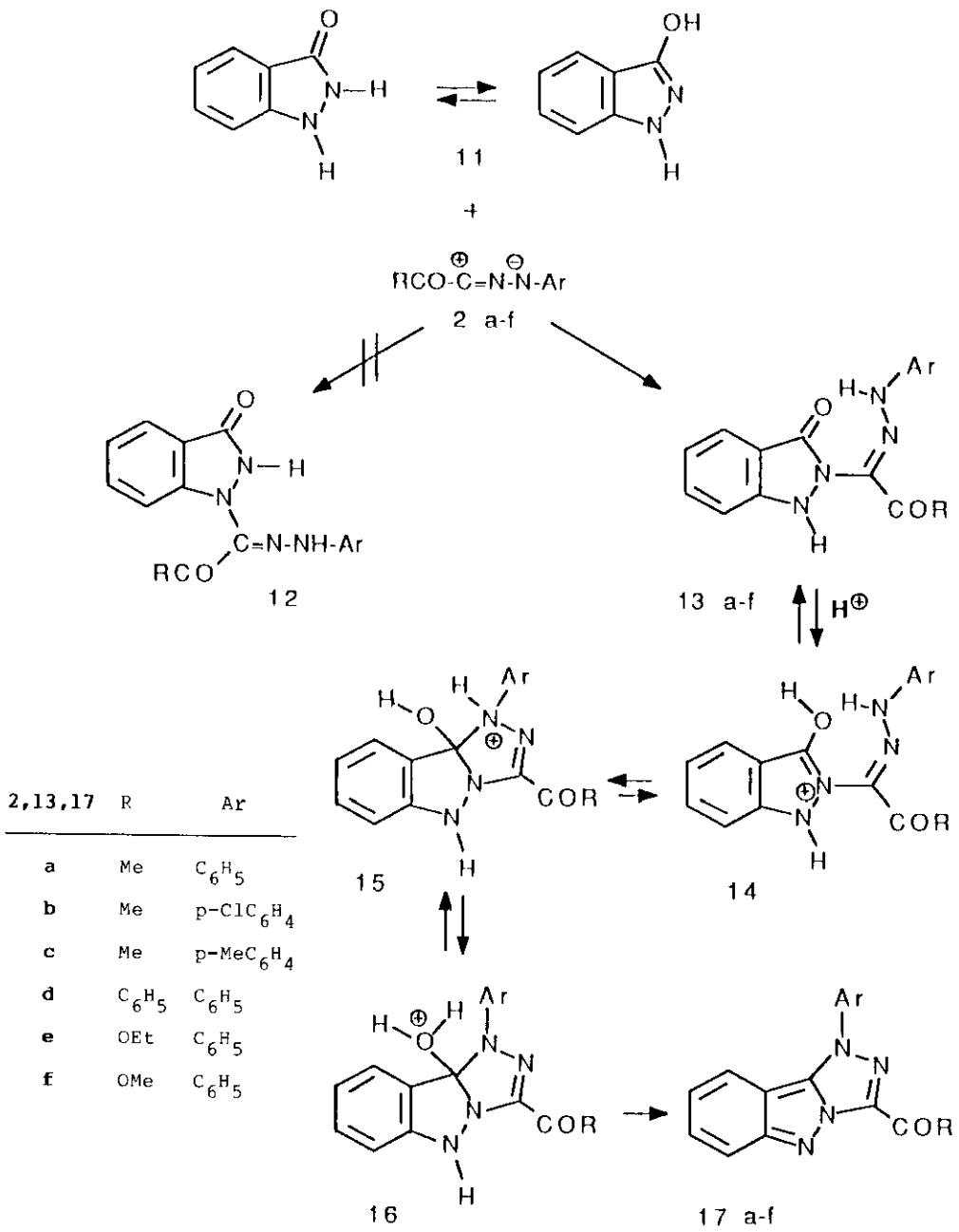
Scheme 1

On the basis of the preceeding results, the 1,3-addition reaction of nitrilimines with the hydroxy form of the 3-indazolinone **11** could allow the formation of the 2-acylindazole arylhydrazone derivatives **13**. The acid induced electrocyclic ring closure of the adducts **13** to **15**, followed by elimination of water could provide a good route for the synthesis of the 1H-1,2,4-triazolo[4,3-b]indazole ring system **17** (see **Scheme 2**).

Actually, the reaction of 3-indazolinone **11** with equimolar amounts of the suitable hydrazidoyl chloride in the presence of a threefold excess of triethylamine for 3 h at room temperature in THF gave the corresponding arylhydrazone derivatives **13a-f** in good yield (see **Table** 1). The analytical and the available spectral data of the obtained compounds (see **Table 2**) are in agreement with the structure of 2-acylindazole arylhydrazone derivatives **13**. Nevertheless, the isomeric structure **12** was essentially excluded on the basis of the successive intramolecular cyclization into the expected 1,2,4-triazolo-[4,3-b]indazoles **17**.

The acid catalyzed cyclization of the arylhydrazones **13a-f** was carried out by refluxing in alcohol containing concentrated hydrochloric acid, and the spectral data of the obtained compounds **17a-f** are shown in **Table 2**. The uv spectra exhibit characteristic absorptions at 263-273, 308-342 and 366-400 nm. In the ir spectra, the C=O stretching absorptions are found in the regions 1725-1730 and 1670-1690 cm^{-1}, depending on the ester or acyl substituent. In the ^1H nmr spectra, the acetyl proton singlets of **17a-c** appear at δ 2.80-2.86 and the two proton multiplet for the ortho protons of the benzoyl group of **17d** resonates at δ 8.40, owing to the deshielding effect of the nitrogen atoms of the heterocyclic ring.

The reported results give further confirmations of the regioselectivity of the 1,3-addition reaction of nitrilimines **2** with the indazole system to give 2-acylindazole arylhydrazone derivatives and represent a further evidence of the usefulness of the addition - rearrangement method for the synthesis of nitrogen containing polycondensed heterocyclic systems.



2,13,17	R	Ar
a	Me	C_6H_5
b	Me	p-ClC_6H_4
c	Me	p-MeC_6H_4
d	C_6H_5	C_6H_5
e	OEt	C_6H_5
f	OMe	C_6H_5

Scheme 2

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra (nujol mull) were recorded on a Perkin-Elmer infrared spectrophotometer (model 297); uv spectra (ethanol) were determined with a Varian Superscan 3 spectrophotometer; mass spectra were recorded on a Jeol OISG-2 spectrometer; ^{1}H nmr spectra were recorded on a Varian EM 360 spectrometer. Chemical shifts are reported as δ values (ppm) relative to TMS as internal standard.

General Method for the Preparation of the Arylhydrazones **13a-f.**

To a suspension of 3-indazolinone **11** (15 mmol) in anhydrous THF (10 ml), a THF solution of suitable hydrazidoyl chloride[8] (15 mmol in 20 ml) and a threefold excess of triethylamine (45 mmol) were added. After stirring at room temperature for 3 h, the resulting insoluble material was filtered off and washed with methanol to dissolve the triethylamine hydrochloride (yield 80-90%). The insoluble material was recrystallized from the appropriate solvent to give arylhydrazones **13a-f.** The THF filtrate was evaporated under reduced pressure and the residue, after treatment with methanol, gave further amounts of **13a-f** (see **Table 1** and **Table 2**).

Cyclization Reactions of the Arylhydrazones **13a-f** - Synthesis of 3-Acyl- and 3-Alkoxycarbonyl-1-aryl-1H-1,2,4-triazolo[4,3-b]indazole derivatives **17a-f.**

To a suspension of **13a-d** (3 mmol) in n-butanol (100 ml), hydrochloric acid (36%, 1.5 ml) was added and the mixture was refluxed for 3 h (see **Table 1**). In the case of the hydrazones **13e** and **13f**, the solvent was ethanol or 1,4-dioxane, respectively. Evaporation under reduced pressure of the reaction mixture gave a residue which taken up with methanol (ethanol for **13e**) and filtered off. Recrystallization from the appropriate solvent gave the 3-acyl- and 3-alkoxycarbonyl-1-aryl-1H-1,2,4-triazolo[4,3-b]indazole derivatives **17a-f** (see **Table 1** and **Table 2**).

TABLE 1. Synthesis of **13** and Cyclization Reactions to **17.**

	R	Ar	Reaction Time (hours)	Yield[a] (%)	mp(°C) (solvent)	Analysis Calcd.(Found) C (%)	H (%)	N (%)	Molecular Formula	Ms (75 eV) m/e
13a	Me	C_6H_5	3	73	243 (butanol)	66.29 (66.21)	4.79 (4.82)	19.04 (18.98)	$C_{16}H_{14}N_4O_2$	294
13b	Me	p-ClC_6H_4	3	76	252 (butanol)	58.46 (58.53)	3.99 (4.03)	17.04 (17.12)	$C_{16}H_{13}ClN_4O_2$	328
13c	Me	p-MeC_6H_4	3	83	243 (butanol)	66.22 (66.37)	5.23 (5.20)	18.17 (18.23)	$C_{17}H_{16}N_4O_2$	308
13d	C_6H_5	C_6H_5	3	81	240 (butanol)	70.77 (70.68)	4.53 (4.60)	15.72 (15.68)	$C_{21}H_{16}N_4O_2$	356
13e	OEt	C_6H_5	3	63	222 (1,4-dioxane)	62.95 (62.90)	4.97 (5.02)	17.28 (17.22)	$C_{17}H_{16}N_4O_3$	324
13f	OMe	C_6H_5	3	50	224 (1,4-dioxane)	61.93 (62.01)	4.55 (4.52)	18.06 (17.99)	$C_{16}H_{14}N_4O_3$	310
17a	Me	C_6H_5	3	80	210 (butanol)	69.55 (69.59)	4.38 (4.36)	20.28 (20.31)	$C_{16}H_{12}N_4O$	276
17b	Me	p-ClC_6H_4	3	72	222 (butanol)	61.85 (61.81)	3.57 (3.52)	18.03 (17.91)	$C_{16}H_{11}ClN_4O$	310
17c	Me	p-MeC_6H_4	3	74	195 (butanol)	70.33 (70.41)	4.86 (4.81)	19.30 (19.35)	$C_{17}H_{14}N_4O$	290
17d	C_6H_5	C_6H_5	3	84	193 (butanol)	74.54 (74.55)	4.17 (4.20)	16.56 (16.67)	$C_{21}H_{14}N_4O$	338
17e	OEt	C_6H_5	10	26	224 (ethanol)	66.66 (66.59)	4.61 (4.63)	18.29 (18.26)	$C_{17}H_{14}N_4O_2$	306
17f	OMe	C_6H_5	4	50	213 (methanol)	65.75 (65.69)	4.14 (4.17)	19.17 (19.23)	$C_{16}H_{12}N_4O_2$	292

[a] Yield calculated on recrystallized product.

TABLE 2. Spectral Data for Compounds **13** and **17**.

	ir (nujol) ν (cm^{-1})	uv (ethanol) λ_{max}, nm (logε)	^{1}H nmr ($CDCl_3$) δ (ppm)
13a	3220, 3180 (NH) 1655 (C=O) 1615, 1595 (C=N)	219(4.43), 230s(4.38), 295s(3.91) 341 (4.37)	[a]
13b	3250, 3160 (NH) 1660 (C=O) 1620, 1595 (C=N)	219(4.41), 230s(4.33) 303s(4.11), 347 (4.39)	[a]
13c	3240, 3200 (NH) 1655 (C=O) 1615, 1595 (C=N)	219(4.43), 230s(4.37), 291s(3.88) 302s(3.99), 350 (4.37)	[a]
13d	3240, 3210 (NH) 1655 (C=O) 1615, 1595 (C=N)	218(4.47), 240s(4.33) 362 (4.30)	[a]
13e	3240, 3100 (NH) 1670, 1650 (C=O) 1615, 1600 (C=N)	219(4.43), 228s(4.37), 295s(3.98) 330 (4.36)	[b] 1.20(t,3H,O-$CH_2\underline{CH_3}$,J=7Hz) 4.15(q,2H,O-$\underline{CH_2}CH_3$,J=7Hz) 6.8-7.8(m,9H,Ar$\underline{H}$)[3] 10.20, 10.90(2 bs,2H,2x$\underline{NH}$)
13f	3240, 3220 (NH) 1680, 1655 (C=O) 1615, 1600 (C=N)	219(4.48), 228s(4.42), 295s(4.03) 330 (4.37)	[b] 3.70(s,3H,OMe) 6.8-7.8(m,9H,Ar$\underline{H}$) 10.20, 10.90(2 bs,2H,2x$\underline{NH}$)
17a	1677 (C=O) 1632, 1598 (C=N)	228(4.35), 269(4.19), 285s(4.11) 319(3.99), 329(4.01), 379(3.80)	2.80(s,3H,COMe), 6.8-8.0(m,9H,Ar$\underline{H}$)
17b	1690 (C=O) 1630, 1590 (C=N)	225s(4.41),271(4.31), 283s(4.25) 318(4.07), 328(4.07), 381(3.90)	2.86(s,3H,COMe), 6.8-8.0(m,8H,Ar$\underline{H}$)
17c	1690 (C=O) 1630 (C=N)	226(4.36), 273(4.23), 286s(4.17) 320(4.03), 330(4.05), 381(3.85)	2.45(s,3H,p-Me), 2.80(s,3H,COMe), 6.7-7.9(m,8H,Ar$\underline{H}$)
17d	1670 (C=O) 1640 (C=N)	231(4.42), 269(4.38), 296s(4.19) 332(4.13), 342(4.14), 400(3.90)	6.8-8.1(m,12H,Ar$\underline{H}$) 8,40(m,2H,$\underline{ortho}$-$\underline{H}$ of $COC_6\underline{H}_5$)
17e	1725 (C=O) 1630, 1595 (C=N)	224(4.44), 263(4.27), 280s(4.10) 308(4.01), 315(4.02), 366(3.91)	1.50(t 3H,O-$CH_2\underline{CH_3}$,J=7Hz) 4.65(q,2H,O-$\underline{CH_2}CH_3$,J=7Hz) 6.7-8.0(m,9H,Ar$\underline{H}$)[3]
17f	1730 (C=O) 1630, 1595 (C=N)	225(4.49), 263(4.33), 280s(4.18) 308(4.06), 315(4.07), 370(3.95)	4.18(s,3H,OMe) 6.8-8.0(m,9H,Ar$\underline{H}$)

[a] The very low solubility did not allow the record of the spectrum.

[b] In DMSO-d_6.

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