Synthesis of *N*-(5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)acetamides using the Ritter reaction

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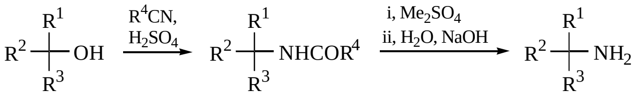
Aromatic *tert*-alkylamines and *N*-(5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)acetamides were successfully prepared using the Ritter reaction under mild dilute conditions.

Aliphatic tertiary alkyl amines are extensively used in constructing biologically active molecules.[1] The Ritter reaction[2] with hydrogen cyanide in acidic media followed by hydrolysis of the resulting amide is a useful and practical way to obtain alkylamines[3] from more readily available alcohols. Nevertheless, the synthesis of *tert*-alkylamines under classical Ritter conditions (acetic acid, sulfuric acid, 50 °C) is restricted due to competitive elimination and requires the use of milder conditions.[4] Moreover, the use of highly toxic alkali metal cyanides in an acidic medium requires careful handling.



1 **2** **3**

Scheme 1

We used the Ritter reaction with acetonitrile under dilute conditions followed by amide methylation and hydrolysis[5] (Scheme 1) for the synthesis of *tert*-alkylamines which cannot be prepared under classical Ritter conditions. We also applied the dilute conditions to the synthesis of previously unknown *N*-[1-(*tert*-butyl)-3,4-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl]acetamides expected to be potent herbicides.[6] The key factors affecting the amide yield are the initial alcohol concentration and the acidity. The greater is the excess of acetonitrile, the higher is the amide yield provided that the initial quantity of sulfuric acid is low and constant (Table 1).

Under classical conditions, the reaction of 2-(3-chlorophenyl)-propan-2-ol **1a** ($R^1 = R^2 = Me$, $R^3 = 3\text{-ClC}_6H_4$) with acetonitrile does not lead to 2-(3-chlorophenyl)-2-acetamidopropane **2a** at all (Table 1, run 1); the products were substituted indans and chain styrene dimers easily formed from **1a** under acidic conditions.[7] The dilution of the initial reaction mixture with MeCN in the absence of AcOH drastically enhanced the formation of **2a** (run 2), and it became predominant at a 0.2 mol dm^{-3} initial concentration of **1a**. If the concentration of **1a** was 0.1 mol dm^{-3} or lower (runs 4 and 5), **2a** became the only product in the form of sulfate **4a**, which can be easily isolated by filtration.

Table 1 Reaction of **1a** with MeCN under Ritter (run 1) and dilute conditions.[a]

Run	Initial concentration of **1a**/ mol dm^{-3}	Yield of **4a** (%)	Total yield of **2a** (%)
1	1.25	—	0[b]
2	0.625	19	20
3	0.42	33	38
4	0.2	50	60
5[c]	0.1	61	80

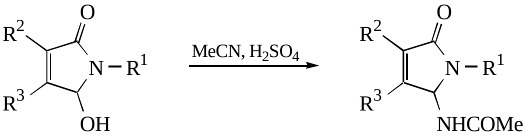
[a] *Ritter conditions*: **1a** (5 mmol), acetic acid (2 ml), sulfuric acid (1 ml), MeCN (10 mmol, 0.5 ml), 60 °C. *Dilute conditions*: **1a** (5 mmol), sulfuric acid (15 mmol), MeCN (according to Table 1), 20–25 °C. [b] 3-Chloro-α-methylstyrene dimers are formed. [c] *Procedure*: to a solution of **1a** (0.85 g, 5 mmol) in acetonitrile (50 ml, 1 mol) sulfuric acid (1.47 g, 15 mmol) was added, and the reaction mixture was stirred for 2 h at ambient temperature. Salt **4a** (0.94 g, yield 61%) was filtered off as a solid;[6] water (10 ml) was added, and the mixture was extracted with ethyl acetate; **2a** (0.64 g, 61%) was isolated. The acetonitrile filtrate was neutralised with triethylamine (3 g, 30 mmol), concentrated and extracted with ethyl acetate; additional amide **2a** (0.20 g, yield 19%) was isolated as a solid: mp 114 °C, ^1H NMR ($CDCl_3$) δ: 1.63 (s, 6H), 1.94 (s, 3H), 5.98 (br. s, 1H), 7.1–7.4 (m, 4H).

Table 2 Preparation of amides **2** from alcohol **1** under dilute conditions (Scheme 1).

Run	R^1	R^2	R^3	R^4	Time/h	Product	Yield (%)
1	3-ClC_6H_4	Me	Me	Me	24	**2a**	86
2	3-ClC_6H_4	Me	Me	$PhCH_2$	96	**2b**	60
3	$3,5\text{-Cl}_2C_6H_3$	Me	Me	Me	24	**2c**	84
4	Ph	Me	Me	Me	24	**2d**	6
5	Me	Me	Me	Me	24	**2e**	68
6	Me	H	H	Me	24	—	0
7	H	H	H	Me	24	—	0

Examples of the preparation of *N*-alkylamides **2** from alcohols **1** are summarised in Table 2. Under dilute conditions (0.1 M solutions of starting alcohols), *N*-*tert*-alkylamides **2a**–**c**,**e** were prepared in high yields (runs 1–3 and 5), but primary alkylamides (runs 6 and 7) could not be obtained. We found that phenylacetonitrile (run 2) can be employed as a nitrogen nucleophile under dilute conditions.

Unfortunately, 2-phenyl-2-acetamidopropane **2d** (run 4) was not obtained preparatively even under dilute conditions because of elimination and irreversible formation of α-methylstyrene dimers.[7] The difference may be accounted for a lower electrophilic activity of the carbocation formed from **2d**.



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Scheme 2

The reaction under dilute conditions appeared to be indispensable for the preparation of potentially biologically active *N*-(5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)acetamides **5** (Scheme 2). The syntheses of previously unavailable compounds **5** in high yields are summarised in Table 3.

Table 3 Preparation of **5** from corresponding 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones (MeCN, 0.1 M solution of the starting compound, 0.3 M H_2SO_4, 24 h, ambient temperature).

Run	R^1	R^2	R^3	Yield of **5** (%)
1	Bu^t	Me	Me	91[a]
2	$PhCH_2$	$R^2 + R^3$ = –CH=CH–CH=CH–		88
3	DDB[b]	Me	Me	98
4	DDB	2-FC_6H_4	Me	93
5	DDB	Ph	Me	95

[a] To a solution of 1-(*tert*-butyl)-5-hydroxy-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (0.376 g, 2 mmol) in MeCN (25 ml) sulfuric acid (0.6 g, 6 mmol) was added, the mixture was stirred at room temperature for 24 h, triethylamine (2 ml) was added, the mixture was evaporated, extracted with ethyl acetate, washed with water and aqueous $NaHCO_3$ and dried. *N*-[1-(*tert*-Butyl)-3,4-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl]acetamide (0.41 g, 91%) was isolated as a solid: mp 169 °C; ^1H NMR ($CDCl_3$) δ: 1.38 (s, 9H), 1.64 (s, 3H), 1.79 (s, 3H), 2.02 (s, 3H), 5.89 (d, 1H, 9.5 Hz), 6.35 (d, 1H, 9.5 Hz, exchangeable); IR (KBr, ν/cm^{-1}): 1223, 1256, 1375, 1526, 1665, 3294; MS, *m*/*z*: 225 (M + 1). [b] α,α-Dimethyl-3,5-dichlorobenzyl.

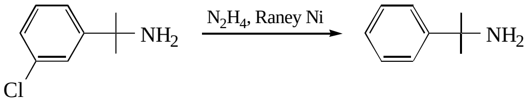
Table 4 Preparation of *tert*-alkylamines **3a**,**c**–**e** from amides **2** (Scheme 1).[a]

Run	R^1	R^2	R^3	Product	Yield of **3** (%)
1	3-ClC_6H_4	Me	Me	**3a**	72
2	3,5-$Cl_2C_6H_3$	Me	Me	**3c**	70
3	Ph	Me	Me	**3d**	77[b]
4	Me	Me	Me	**3e**	71

[a] *Hydrolysis*: to **2a** (1.055 g, 5 mmol) dimethyl sulfate (4 g, 32 mmol) was added, and the mixture was stirred for 1 h at 80 °C. Next, the excess of dimethyl sulfate was distilled at a reduced pressure. Water (3 ml) was added, the mixture was filtered, extracted with toluene (50 ml), basified to pH 12 with solid sodium hydroxide and extracted with hexane (3×5 ml). The extract was dried with NaOH and distilled at 75–80 °C (1 mmHg) to give **3a** (0.61 g, yield 72%). ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 6H), 1.60 (s, 2H), 7.1–7.5 (m, 4H).

[b] Prepared by reduction of **3a** with the hydrazine: **3a** (0.5 g, 2.9 mmol), MeOH (3 ml), hydrazine hydrate (1 ml, 30 mmol) and potassium hydroxide (0.5 g, 9 mmol) were stirred with Raney Ni (0.10 g) for 4 h; the mixture was concentrated, extracted with hexane, dried with NaOH and evaporated to give **3d** (0.30 g, yield 77%). ^{1}H NMR ($CDCl_3$) δ: 1.51 (s, 6H), 1.62 (s, 2H), 7.2–7.4 (m, 3H), 7.5–7.7 (m, 2H).

N-*tert*-Alkylamines **3a**–**d** were prepared by methylation and hydrolysis of amides **2a** in high yields (Table 4). Since **2c** was not available, corresponding amine **3d** was obtained *via* the catalytic (Raney nickel) reduction of **3a** with hydrazine (Scheme 3).



3a **3d**

Scheme 3

Thus, the Ritter reaction in the presence of a 200-fold excess of a nitrile proceeds selectively under mild conditions and can be useful for the synthesis of branched alkylamines and *N*-pyrrolylacetamides.

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