A facile synthesis of acylhydrazines from acylbenzotriazoles

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Acylbenzotriazoles were found to react with substituted hydrazines and aqueous hydrazine under very mild conditions, thus affording a facile synthesis of three types of acylhydrazines in moderate to excellent yields.

Keywords: acylbenzotriazoles, acylhydrazines, acylation, hydrazinolysis

Acylhydrazines[1] and their metal complexes[2] have been found to possess a variety of biological activities. They are also frequently used as starting materials for the synthesis of heterocyclic compounds[3] and multisubstitued hydrazines.[4]

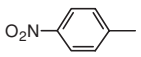
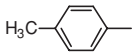
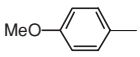
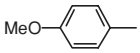
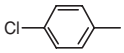
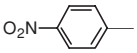
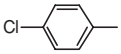
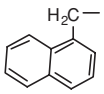
Generally, acylhydrazines are prepared by the acylation of hydrazines with acylchlorides,[5] anhydrides or esters.[6] A carboxylic acid was recently used for a direct conversion of hydrazines into acylhydrazides with lipase as the catalyst,[7] but kinetic studies and mechanism were the major focus of the work and only a few compounds were prepared. We report here a facile synthesis of acylhydrazines with acylbenzotriazoles as the acylating reagents.

Reports concerning the application of acylbenzotriazoles as neutral acylating reagents recently drew our attention. Acylbenzotriazoles, being stable and crystalline solids, are easily available from the corresponding carboxylic acids, including those whose acyl halides are not easy to prepare, thus affording a considerable advantage.[8a] They are especially efficient *N*-acylating agents. For example, They have been used in peptide chemistry for decades,[8b,c] and were successfully used for the preparation of formamides,[8d] trifluoroacetamides[8e] and oxamides.[8f] Recently, a general preparative method was developed for primary, secondary and tertiary amides, which resulted from the acylation with acylbenzotriazoles of ammonia or the primary or secondary amines respectively.[9a] The efficient conversion of carboxylic acids into unsubstituted *N*-alkyl-, *O*-alkyl-, and *O*,*N*-dialkylhydroxamic acids via acylbenzotriazole intermediates was also realized by selective acylation of the nitrogen atom in hydroxylamine.[9b] We now wish to report a general synthesis of acylhydrazines by the acylation of hydrazines with acylbenzotriazoles.

Although the formation of cinnamoyl hydrazides by such a method was known, the reactants were limited to acylbenzotriazoles derived from α,β-unsaturated carboxylic acids and anhydrous hydrazine.[9c] The possibility of acylation of *N*-substituted hydrazines and also aqueous hydrazines with acylbenzotriazoles derived from ordinary carboxylic acids as acylating reagents was hitherto unexplored.

Firstly, our investigation found that acylbenzotriazoles could acylate *N*-aryl hydrazines in THF with reasonable to good yields at room temperature without any additives as promoters (Scheme 1, Table 1).

Table 1 Synthesis of *N*-aryl-*N*′-acylhydrazines

Entry	R	Ar	Product	Yield/%[a]	M.p./°C	
					Found	lit.
1			**2a**	76	166–167	167–168[10]
2			**2b**	55	191–193	195–196[11]
3			**2c**	73	168–169	166–167[10]
4			**2d**	70	176–177	177–178[10]
5			**2e**	68	195–197	194–196[11]
6			**2f**	86	198–200	200–201[12]
7			**2g**	83	186–188	188–190[13]
8			**2h**	62	236–238	240[14]
9			**2i**	68	225–227	–[b]
10	$H_3C–CH_2–$		**2j**	55	157–159	158–159[15]

[a]Isolated yields based on hydrazines with a reaction time of 5 hours. [b]Novel compound.

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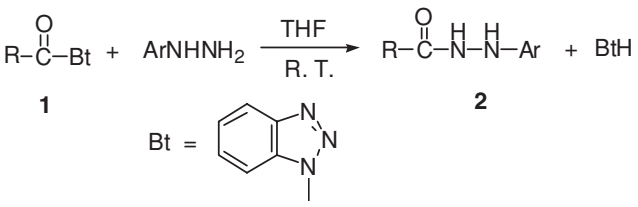


Scheme 1

Subsequent investigation found that acylbenzotriazoles could acylate aqueous hydrazine (80%) in excellent yield (Scheme 2, Table 2). The presence of water, which may interfere as a competing nucleophile, causes non-productive hydrolysis of the acylbenzotriazoles.

Finally, the diacylation of aqueous hydrazine with acylbenzotriazoles was investigated. When two equivalents of acylbenzotriazole were introduced into the reaction system, and after stirring at room temperature for 24 h, the anticipated *N,N*-diacylhydrazines precipitated with moderate yields (Scheme 3).

In conclusion, the reaction conditions required for the acylation of substituted hydrazines and aqueous hydrazine with acylbenzotriazoles prove very mild, and no extra additives were needed to promote the acylating process. Together with the ready availability of acylbenzotriazoles and the good to excellent yields of the products, the method described here may be an attractive one for the synthesis of acylhydrazines.

Experimental

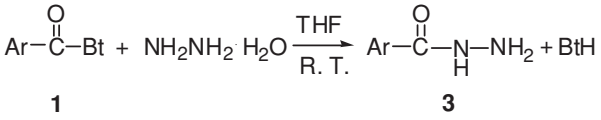
General. ^{1}H NMR spectra were recorded on a Bruker AC-400 instrument as $CDCl_3$ or DMSO solutions using TMS as an internal standard. Chemical shifts (δ) were reported in ppm and coupling constants *J* are given in Hz. IR spectra were recorded using KBr disks with a Bruker Vector-22 infrared spectrometer. Elemental analyses were performed on an EA-1110 instrument. Melting points are uncorrected. Hydrazines were commercially available and acylbenzotriazoles were synthesized according to literature procedures. [9a]

CAUTION: Hydrazines are a class of hazardous reagents and careful attention should be made so as not to make any skin contact with them!

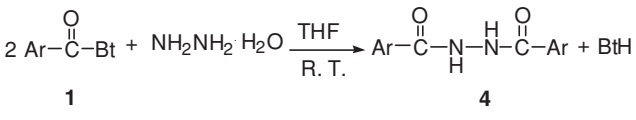
General procedure for the acylation of N-arylhydrazines with acylbenzotriazoles: A mixture of the arylhydrazine (1 mmol) and acylbenzotriazole (1 mmol) in THF (10 ml) was stirred at room temperature for a fixed time (the reaction time was indicated in Table 1). After THF was removed under reduced pressure, the residue was dissolved in ethyl acetate (15 ml). The organic layer was washed successively with saturated aqueous Na_2CO_3 and H_2O, dried over anhydrous $MgSO_4$, and then evaporated to give a crude product, which was either recrystallised from EtOH or purified by preparative TLC on silica gel using ethyl acetate–cyclohexane (1:1) as eluent to afford pure acylhydrazine **2**.

General procedure for the monoacylation of aqueous hydrazine with acylbenzotriazoles: A mixture of aqueous hydrazine (80%, 0.063g, 1 mmol) and acylbenzotriazole (1 mmol) in THF (10 ml) was stirred at room temperature for 15 min. Removal of the solvent afforded a residue, which was purified by preparative TLC on silica gel using ethyl acetate–cyclohexane (1:1) as eluent to afford pure acylhydrazine **3**.

General procedure for the diacylation of aqueous hydrazine with acylbenzotriazoles: A mixture of aqueous hydrazine ((80%, 0.063g, 1 mmol) and acylbenzotriazole (2 mmol) in THF (10 ml) was stirred at room temperature for 24 h. The precipited product was filtered and washed with cold methanol to afford *N, N'*-diaroylhydrazine **4**. The filtrate was mixed with aqueous Na_2CO_3 (2 ml) and extracted with benzene. The extracts were dried over anhydrous $MgSO_4$ and evaporated to give a residue, which was crystallised from methanol or ethanol to afford another portion of the corresponding compound **4**.

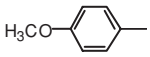
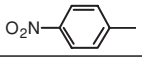


Scheme 2



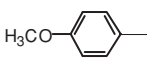
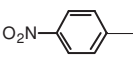
Scheme 3

Table 2 Monoacylation of aqueous hydrazine with acylbenzotriazoles

Entry	Ar	Product	Yield/%[a]	M.p./°C	
				Found	Lit. [12]
1		**3a**	95	113–114	112–113
2		**3b**	93	136–138	136
3		**3c**	96	219–210	210

[a]Isolated yields based on the hydrazine with a reaction time of 15 min.

Table 3 Diacylation of aqueous hydrazine with acylbenzotriazoles

Entry	Ar	Product	Yield/%[a]	M.p./°C	
				Found	Lit. [12]
1		**4a**	**65**	238–240	241
2		**4b**	60	220–222	224
3		**4c**	57	247–249	245

[a]Isolated yields based on the hydrazines with the reaction time prolonged to 24 h.

Melting points of products (except **2i**) are compared with literature values in the tables.

2a: White needles. ν_{max}(KBr)/cm^{-1}: 3324, 3257, 3052, 1646, 1600. ^{1}H NMR δ_H ($CDCl_3$): 7.93 (br, s, 1H), 7.84 (d, 2H, *J* = 8.0 Hz), 7.46–7.59 (m, 3H), 7.23–7.27 (m, 2H), 6.91–6.94 (m, 3H), 6.35 (br, d, 1H, *J* = 3.6 Hz).

2b: Yellow needles. ν_{max}(KBr)/cm^{-1}: 3323, 3232, 3076, 1630, 1603. ^{1}H NMR δ_H (DMSO): 10.64 (br, s, 1H), 9.18 (br, s, 1H), 6.79–8.02 (m, 9H).

2c: White solid. ν_{max}(KBr)/cm^{-1}: 3317, 3244, 3019, 2913, 2846, 1646, 1607. ^{1}H NMR δ_H ($CDCl_3$): 7.80 (br, s, 1H), 7.75 (d, 2H, *J* = 8.0 Hz), 7.23–7.31 (m, 4H), 6.91–6.95 (m, 3H), 6.31 (d, 1H, *J* = 4.0 Hz), 2.43 (s, 3H).

2d: White solid. ν_{max}(KBr)/cm^{-1}: 3321, 3264, 3059, 3001, 2956, 2932, 2837, 1638, 1605. ^{1}H NMR δ_H ($CDCl_3$): 7.82 (d, 2H, *J* = 8.8 Hz), 7.83 (s, 1H), 7.23–7.26 (m, 2H), 6.90–6.98 (m, 5H), 6.33 (d, 1H, *J* = 4.0 Hz), 3.87 (s, 3H).

2e: White solid. ν_{max}(KBr)/cm^{-1}: 3365, 3245, 3067, 3000, 1646, 1605. ^{1}H NMR δ_H (DMSO): 10.25 (br, s, 1H), 8.06 (s, 1H), 7.88 (d, 2H, *J* = 8.0 Hz), 6.76–7.79 (m, 6H) 3.84 (s, 3H).

2f: Yellow solid. ν_{max}(KBr)/cm^{-1}: 3361, 3293, 3111, 1638, 1600. ^{1}H NMR δ_H ($CDCl_3$): 8.35 (d, 2H, *J* = 8.8 Hz), 8.02 (d, 2H, *J* = 8.8 Hz), 8.04 (br, s, 1H), 7.26–7.30 (m, 2H), 6.93–6.99 (m, 3H), 6.35 (br, d, 1H, *J* = 4.0 Hz).

2g: White solid. ν_{max}(KBr)/cm^{-1}: 3352, 3251, 3019, 1644, 1593. ^{1}H NMR δ_H ($CDCl_3$): 7.91 (br, s, 1H), 7.71–7.83 (m, 2H), 6.90–7.55 (m, 7H), 6.31 (br, d, 1H, *J* = 2.8 Hz).

2h: White solid. ν_{max}(KBr)/cm^{-1}: 3346, 3250, 1639, 1586, 1534. ^{1}H NMR δ_H ($CDCl_3$): 8.32–8.34 (m, 1H), 7.25–8.00 (m, 9H), 6.90–7.01 (m, 3H), 6.46 (d, 1H, *J* = 4.0 Hz).

2i: White solid. ν_{max}(KBr)/cm^{-1}: 3320, 3257, 1653, 1600. ^{1}H NMR δ_H ($CDCl_3$): 8.02 (d, 1H, *J* = 8, 0 Hz), 7.48–7.93 (m, 6H), 6.81–7.12 (m, 4H), 6.56 (d, 2H, *J* = 8, 4 Hz), 5.94 (d, 1H, *J* = 3.6 Hz), 4.14 (s, 2H). *m/z*(%): 276 (M^+, 15.21), 184 (2.75), 168 (5.64), 141 (57.90), 108 (100.00). Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.2; H, 5.8; N, 10.14. Found C, 78.35; H, 5.9; N, 10.11%.

2j: White solid. ν_{max}(KBr)/cm^{-1}: 3291, 3244, 3032, 2979, 2925, 1633, 1587. ^{1}H NMR δ_H ($CDCl_3$): 7.21–7.26 (m, 2H), 6.77–6.95 (m, 4H), 6.12 (s, 1H), 2.28 (q, 2H, *J* = 5.2 Hz), 1.23 (t, 3H, *J* = 5.2 Hz).

3a: White solid. ν_{max}(KBr)/cm^{-1}: 3297, 3217, 3012, 2872, 1666, 1619, 1566. ^{1}H NMR δ_H ($CDCl_3$): 7.74 (d, 2H, *J* = 8.2 Hz), 7.58 (br, s, 1H), 7.41–7.54 (m, 3H), 4.12 (s, 2H).

3b: White solid. ν_{max}(KBr)/cm^{-1}: 3310, 3211, 2959, 2839, 1646, 1620, 1573. ^{1}H NMR δ_H (DMSO): 9.61 (s, 1H), 7.80 (d, 2H, *J* = 8.8 Hz), 6.98 (d, 2H, *J* = 8.8 Hz), 4.44 (s, 2H), 3.80 (s, 3H).

3c: Yellow solid. ν_{max}(KBr)/cm^{-1}: 3332, 3277, 3118, 3110, 1646, 1620, 1598. ^{1}H NMR δ_H ($CDCl_3$): 8.33 (d, 2H, *J* = 8.8 Hz), 7.93 (d, 2H, *J* = 8.8 Hz), 7.43 (br, s, 1H), 4.17 (br, s, 2H).

4a: White solid. ν_{max}(KBr)/cm^{-1}: 3310, 3211, 2959, 2839, 1646, 1620, 1573. ^{1}H NMR δ_H (DMSO): 10.25 (br, s, 2H), 7.93 (d, 4H, *J* = 7.2 Hz), 7.50–7.61 (m, 6H).

4b: White solid. ν_{max}(KBr)/cm^{-1}: 3219, 3197, 2846, 1613, 1573. ^{1}H NMR δ_H (DMSO): 10.30 (br, s, 2H), 7.90 (d, 4H, *J* = 8.8 Hz), 7.05 (d, 4H, *J* = 8.8 Hz), 3.83 (s, 6H).

4c: Orange solid. ν_{max}(KBr)/cm^{-1}: 3209, 3039, 2853, 1621, 1583. ^{1}H NMR δ_H (DMSO): 11.04 (s, 2H), 8.39 (d, 4H, *J* = 8.8 Hz), 8.16 (d, 4H, *J* = 8.8 Hz).

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