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3-Acyl-1,3-diaryltriazenes as neutral and selective acylating agents

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Abstract—New 3-acyl-1,3-diaryltriazenes have been prepared and their reactions with amino compounds have been studied. Reactions proceed rapidly under mild conditions to give the corresponding *N*-acyl products. Reagents enable chemoselective acylation of aliphatic primary and secondary amines in the presence of other acylable functional groups.

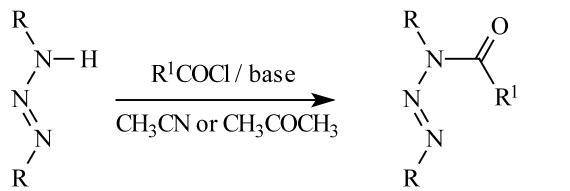
Many different acylating reagents have appeared in the literature,[1] of which chemoselective ones are most desired.

A few years ago we reported on a simple conversion of aromatic amines mediated by $Na_3Co(NO_2)_6$[2] which resulted in the formation of the corresponding triazenes. The procedure enables a very convenient preparation of various 1,3-diaryltriazenes, a class of compounds from which representatives are known to possess anorectic activity.[3] They were also used as starting materials for the preparation of 1,3-diaza-2-azoniaallene salts, novel N_3-building blocks.[4] As we described earlier, the failure to obtain the complete ^{13}C NMR spectra of several 1,3-diaryltriazenes required the methylation of the triazene function.[2] Alternatively *N*-acyl derivatives can be prepared for the same purpose. The stability of the latter compounds in solution strongly depends on their structure. We have observed two main pathways of decomposition. The first, well-known in the literature, is the heterolytic cleavage[5] of the N(2)–N(3) bond to generate a diazonium ion from N(1)–N(2) residue and an amide species from N(3). The second pathway proceeds by the cleavage of the N(3)–acyl bond, leading to the formation of a 1,3-diaryltriazene.

The last process offers an opportunity to transfer the acyl fragment from the acyltriazene to the appropriate nucleophilic center in another molecule. To the best of our knowledge, such transformation has not yet been observed, and is therefore the subject of the present study.

Herein, we report the synthesis and the application of 3-acyl-1,3-diaryltriazenes **1a–b** and **2a–c**, which are easily prepared in good to moderate yields by the reaction of 1,3-diaryltriazenes **1** and **2** with the corresponding acyl chlorides in acetonitrile or acetone solution in the presence of sodium carbonate or triethylamine as a base (Scheme 1, Table 1).

At the beginning, we were interested in structure–reactivity relationships. Kinetic measurements of the reaction of **1a** and **2a** with butylamine in deuterated



1 and 2 **1a-b and 2a-c**

R : 1	4-O_2N, 2-ClC_6H_3
2	4-$O_2NC_6H_4$

Scheme 1. Synthesis of 3-acyl-1,3-diaryltriazenes.

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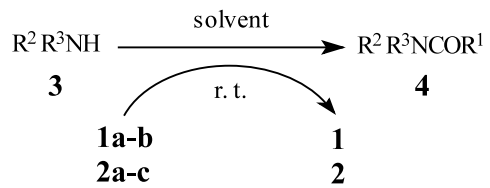
Table 1. Preparation of 3-acyl-1,3-diaryltriazenes

Triazene	R	R^1	Yield (%)	Reaction time (h)
1a[6]	4-O_2N, 2-ClC_6H_3	Me	88	12
1b[7]	4-O_2N, 2-ClC_6H_3	$PhCH_2$	77	24
2a[8]	4-$O_2NC_6H_4$	Me	75	12
2b[9]	4-$O_2NC_6H_4$	$PhCH_2$	50	24
2c[10]	4-$O_2NC_6H_4$	MeO	35	24

chloroform at 25.0±0.1°C indicated that the 4-nitro substituted acetyltriazene **2a** was more reactive than 2-chloro-4-nitro analog **1a** by the factor of 1.8 and relative to the known 3-acetyl-1,3-bis(4-bromophenyl)triazene[8] by a factor of 13.4. It should be noted that the phenylacetyltriazene (benzylcarbonyltriazene) **2b** showed higher reactivity by a factor of 5.7 than its acetyl analog **1a**. The reactions of 3-acyl-1,3-diaryltriazenes with butylamine in deuterated chloroform, monitored by ^1H NMR, did not show any side reactions.

Initial studies with primary and secondary amines (Scheme 2) indicated that the 3-acetyl-1,3-diaryltriazenes **1a** and **2a** provided a chemoselective acetylation of the primary and the secondary aliphatic amino group in the presence of other acetylable functional groups (entries **1**–**4**, Table 2).

Acylation of other amines with **1a** and **2a** are summarized in Table 2. The yields are generally high and reactions terminate without side reactions on hydroxy or aromatic amino groups or heterocyclic NH moieties. Moreover, reactions can be also carried out in methanolic solutions. As it is evident from reaction times (Table 2), the acylation with **2a** proceeds faster than with **1a** being in accord with kinetic observations. An application of the phenylacetyl moiety is playing the part of a convenient protecting group, which can be alternatively removed by enzymatic methods.[11] Despite the high reactivity of the 3-acyl-1,3-diaryltriazenes examined, triazenes **1b** and **2b** are both chemoselective. The above mentioned protecting group can be introduced in the presence of an aromatic $-NH_2$ group (i.e. **4g**), of aliphatic or aromatic –OH groups (i.e. **4a**, **4h** and **4k**), and also in the presence of the –SH group (i.e. **4i**). Applying this method, *N*-protected esters of amino acids can also be prepared (entries **11** and **12**). *N*-Methoxycarbonyl derivatives are the simplest of the carbamate-type protecting groups in common use which were successfully generated using **2c** (entries **13** and **14**, Table 2). Acyl triazenes show great tolerance against hydroxy group, which is clearly evident from the fact that they can even be recrystallized from alcohols (i.e. **1a** and **2b**). Furthermore, one can acylate amino groups in acetonitrile solutions containing water as successfully as in commercially available acetonitrile.



Scheme 2. Acylation of amines.

Triazenes **1a**–**b** and **2a**–**c** were applied on selected amines[12] in 1.1 molar equivalents in methanol, chloroform, or acetonitrile solutions at room temperature, yielding the corresponding *N*-acyl derivatives **4a**–**n** (Table 2) in high yields and excellent chemoselectivity. Furthermore, the procedure is very simple and most of the deacylated triazene can be removed from the reaction mixture and recovered in 80–95% simply by filtration in the case of using methanol or acetonitrile as solvents.

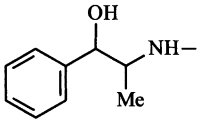
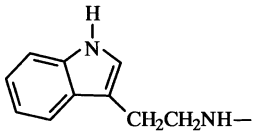
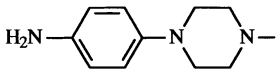
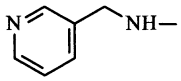
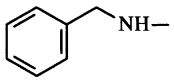
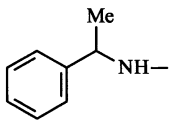
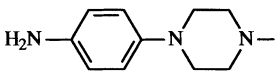
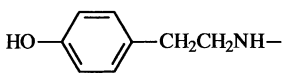
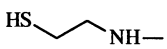
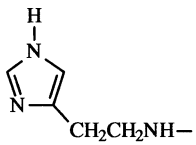
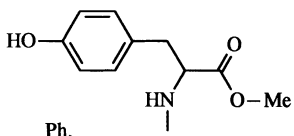
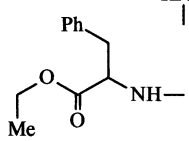
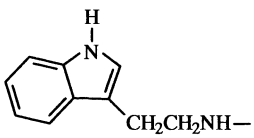
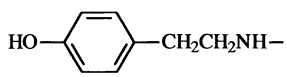
Although one might consider our new reagents for the acylation as related to the 'open-chain' *N*-acylbenzotriazoles described by Katritzky and coworkers,[13] there is a big difference between both types of reagents. Namely, Katritzky and others found that *N*-formylbenzotriazole and *N*-trifluoroacetyl analog can be used for *N*- and *O*-formylation and trifluoroacetylation. Comparing with our reagents, *N*-formylbenzotriazole shows no chemoselectivity due to the fact that *N*- and *O*-formylation with *N*-formylbenzotriazole proceed smoothly at room temperature with high yields.[13a] However, as far as the chemoselectivity of *N*-acylbenzotriazoles is concerned, no study has been made by now.[13c]

In conclusion, 3-acyl-1,3-bis(2-chloro-4-nitrophenyl) triazenes **1a**–**c** and 3-acyl-1,3-bis(4-nitrophenyl)-triazenes **2a**–**c** have been used for the first time as reagents for a chemoselective protection of aliphatic amino groups. They are convenient acylation reagents due to their facile preparation, easy handling, good chemoselectivity and stability. Their reactivity can be easily controlled by the substituents on the aromatic ring.

Acknowledgements

The authors thank Dr. Bogdan Kralj and Dr. Dušan Žigon (Mass Spectrometry Centre, Jožef Stefan Institute, Ljubljana, Slovenia) for mass measurements. The Ministry of Education, Science and Sport of Slovenia (PO–0503–0103) and the Slovenian Science Foundation are gratefully acknowledged for the financial support.

Table 2. Acylation of amines **3** with 3-acyltriazenes **1a–c** and **2a–c**

entry	R^2R^3N–	reagent	solvent	Reaction time (h)	product	yield (%)[a]
1		**1a/2a**	MeOH	53/19	**4a**	97/94
2		**1a/2a**	MeCN	14/5	**4b**	88/98
3		**1a/2a**	〃	24/8	**4c**	91/89
4		**1a/2a**	〃	27/6	**4d**	87/86
5		**1a/2a**	〃	11.5/8	**4e**	91/81
6		**1a/2a**	〃	29/10	**4f**	92/91
7		**1b/2b**	〃	24/8	**4g**	90/98
8		**1b/2b**	MeOH	56/2	**4h**	82/94
9		**1b/2b**	$CHCl_3$	5/4	**4i**	89/96
10		**1b/2b**	〃	8/5	**4j**	81/76
11		**1b/2b**	MeCN	62/48	**4k**	93/81
12		**1b/2b**	〃	84/10	**4l**	96/70
13		**2c**	〃	10	**4m**	81
14		**2c**	MeOH	62	**4n**	86

[a] Isolated yields are given.

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6. Compound **1a**: mp 123–126°C (ethanol); IR (KBr): 3100, 1740, 1525, 1475, 1380, 1350, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.77 (3H, s), 7.43 (1H, d, $J=8.6$ Hz), 7.61 (1H, d, $J=8.6$ Hz), 8.19 (1H, dd, $J_1=8.6$ Hz, $J_2=2.3$ Hz), 8.27 (1H, dd, $J_1=8.6$ Hz, $J_2=2.5$ Hz), 8.33 (1H, d, $J=2.3$ Hz), 8.43 (1H, d, $J=2.5$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.2, 120.7, 123.3, 123.6, 124.7, 125.6, 130.8, 132.4, 133.1, 139.5, 147.5, 148.6, 148.9, 171.9. Anal. calcd for $C_{14}H_9Cl_2N_5O_5$: C, 42.32; H, 2.27; N, 17.63. Found: C, 42.35; H, 2.37; N, 17.34.
7. Compound **1b**: mp 106–108°C (toluene); IR (KBr): 3120, 1735, 1535, 1480, 1360, 1240, 1150, 1130, 1060, 990, 910, 810, 760, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.45 (2H, s), 7.34–7.45 (7H, m), 8.18 (1H, dd, $J_1=8.9$ Hz, $J_2=2.4$ Hz), 8.27 (1H, dd, $J_1=8.9$ Hz, $J_2=2.4$ Hz), 8.33 (1H, d, $J=2.4$ Hz), 8.42 (1H, d, $J=2.4$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 40.6, 120.6, 123.3, 123.5, 124.7, 125.6, 126.9, 128.4, 129.6, 131.1, 132.4, 133.2, 133.8, 139.4, 147.6, 148.6, 148.7, 172.4; MS (FAB) m/z (rel. intensity) 474 (MH^+, 2), 184 (40), 91 (44), 71 (39). Anal. calcd for $C_{20}H_{13}Cl_2N_5O_5$: C, 50.65; H, 2.76; N, 14.77. Found: C, 50.96; H, 2.77; N, 14.66.
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9. Compound **2b**: 1,3-bis(4-nitrophenil)triazene (22 mmol, 6.314 g) was added at rt to the stirred solution of phenylacetyl chloride (24.2 mmol, 3.742 g) in acetone (80 mL) and then triethylamine (24.2 mmol, 2.444 g, 3.39 mL) was slowly added. After stirring the reaction mixture at rt for 24 h, the solid material was filtered off and filtrate evaporated to dryness, treated with water (50 mL), filtered off, washed with water and crystallized from acetone/methanol giving **2b** in 50% yields. Mp 130–132°C (acetone/methanol); IR (KBr): 3105, 2933, 1712, 1608, 1524, 1345, 1231, 1124, 1013, 972, 859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.46 (s, 2H), 7.32–7.41 (m, 7H), 7.56–7.61 (m, 2H), 8.28–8.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.3, 123.4, 125.0, 125.3, 128.0, 129.4, 129.5, 130.6, 133.9, 141.2, 148.5, 148.6, 152.7, 173.4; MS (FAB) m/z (rel. intensity) 406 (MH^+, 40), 107 (23), 91 (26). Anal. calcd for $C_{20}H_{15}N_5O_5$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.53; H, 3.56; N, 17.45.
10. Compound **2c**: methyl chloroformate (0.1 mol, 9.45 g) was slowly added at rt to a stirred suspension of 1,3-bis(4-nitrofenil) triazene (10 mmol, 2.86 g) and potassium carbonate (0.092 mol, 12.82 g) in acetone (60 mL). The reaction mixture was stirred at rt for 20 h, the solid material was filtered off, suspended in water (50 mL) and the insoluble material separated by filtration and crystallized from toluene giving **2c** in 35% yields. Mp 127–129°C (toluene); IR (KBr): 3113, 3081, 1734, 1609, 1522, 1476, 1447, 1217, 1107, 961, 860, 760 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.92 (s, 3H), 7.63–7.74 (M, 4H), 8.30–8.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.2, 123.5, 125.1, 125.2, 130.6, 141.8, 148.4, 148.5, 152.6, 153.6; MS (EI) m/z (rel. intensity) 317 (M^+-28, 30), 196 (92), 166 (20), 150 (62), 122 (1000). Anal. calcd for $C_{14}H_{11}N_5O_6$: C, 48.70; H, 3.21; N, 20.28. Found: C, 48.91; H, 3.20; N, 20.01.
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12. **Reaction of 3-acyl-1,3-diaryltriazenes 1a and 1b and 2a–c with amines**. A selected amine (1 mmol) was added to the solution of 3-acyl-1,3-diaryltriazene (1.1 mmol) in acetonitrile, methanol or chloroform (8 mL). The reaction mixture was stirred at room temperature for 2–84 h (see Table 2). Triazene was filtered off and washed with methanol (2×5 mL). The solution was then evaporated to dryness and the solid material purified on chromatotron using EtOAc:hexane = 1:5 (**4n**), EtOAc:hexane = 3:5 (**4i** and **4l**), MeOH:$CHCl_3$ = 1:25 (**4m**) and MeOH:$CHCl_3$ = 1:10 (**for others**). Compound **4g**: mp 134–136°C (diethyl ether/petroleum ether); IR (KBr): 3420, 3360, 2810, 1650, 1520, 1450, 1420, 1285, 1235, 1165, 1045, 835, 750 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.76–2.84 (4H, m), 3.57–3.60 (4H, m), 3.75 (2H, s), 4.60 (2H, bs), 6.46–6.51 (2H, m), 6.65–6.70 (2H, m), 7.19–7.34 (5H, m); MS (EI) m/z (rel. intensity) 295 (M^+, 100), 176 (27), 147 (65), 120 (43), 91 (35). Anal. calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.57; H, 7.35; N, 14.09. Compound **4h**: mp 114–116°C (diethyl ether/petroleum ether); IR (KBr): 3210, 3060, 1600, 1505, 1430, 1320, 1215, 820, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.58 (3H, s), 2.64 (2H, t, $J=6.8$ Hz), 3.42 (2H, dt, $J_1=J_2=6.8$ Hz), 3.53 (2H, s), 5.33 (2H, bs), 6.68–6.72 (2H, m), 6.85–6.89 (2H, m), 7.15–7.18 (2H, m), 7.28–7.33 (3H, m); ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.6, 40.9, 43.9, 115.5, 127.4, 129.1, 129.5, 129.7, 129.8, 130.3, 134.6, 154.6, 171.2; MS (EI) m/z (rel. intensity) 256 (MH^+, 4), 136 (35), 120 (100), 107 (32), 91 (52), 77 (21). Anal. calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.95. Found: C, 75.45; H, 6.53; N, 5.88.
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