SHORT PAPER

J. Chem. Research (S),
2003, 121-123

Acyl maleic hydrazides as versatile acyl transferring agents†

Sabir H Mashraqui* and Jadhav L Shivaji

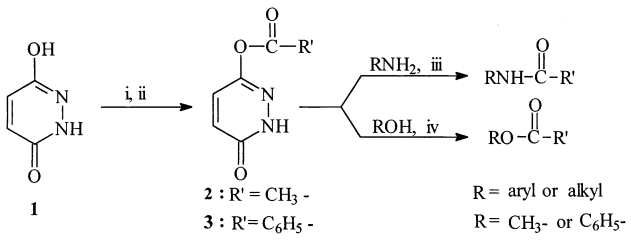
Department of Chemistry, University of Mumbai, Vidyanagari Santacruz (E), Mumbai 400 098, India

Acyl maleic hydrazides have been found to act as effective acyl transferring agents to substrates containing heteroatom nucleophiles such as amines, phenols, alcohols and thiols under mild and convenient conditions.

Keywords: acyl maleic hydrazides, acyl transferring agents

Acylations of amines, phenols and alcohols are widely employed in synthetic organic chemistry for protection, derivatisation and functional group interconversions.[1] Conventionally, acylations are carried out using active acylating agents namely, acid anhydrides and acid chlorides. These acylating agents are unstable, corrosive and toxic in nature and moreover, with the exception of amines, the acylations of phenols, alcohols and thiols are not spontaneous, requiring base, Lewis acid or metal ion catalysis for acylations to occur.[2] On the other hand, acylations via transesterification and aminolysis are preperatively less attractive since being equilibrium processes, they generally afford unsatisfactory conversions.[3–4] Though, a plethora of methods are currently available for acylations,[5–10] there remains a continuing interest to develop new and improved methods to effect acylations under selective and controlled conditions, particularly to meet the ever growing interest in the synthesis of biologically active peptides and sensitive macrolide targets.[4,11]

Although acyl maleic hydrazide derivatives are known in the literature, they seem to have not yet been tested for their acyl transferring potential. We envisaged that maleic hydrazide **1** might function as an acyl carrier on the ground that its high acidity (*pK*a = 13)[12] would render it a good nucleofuge thereby allowing acyl transfers to occur with ease with reactive nucleophiles as illustrated in the Scheme 1. We now report that maleic hydrazide, a commercially inexpensive material can be successfully employed as an acyl carrier to a variety of heteroatom nucleophiles.



Scheme 1 Reagents and conditions: (i) $(CH_3CO)_2O$, reflux, 5h; (ii) C_6H_5COCl, dry pyridine, 0°C–R.T; (iii) RNH_2, DMF, 70–80°C, 2–6h; (iv) ROH, DMF, Et_3N, 70–80°C, 2–6h.

To start with, the known mono-O-acetyl **2**[16] and mono-O-benzoyl maleic hydrazide **3**[17] were prepared as the model acyl carriers by following the literature procedures in 70–75% yields. With acyl maleic hydrazides **2** and **3** in hand, we studied their potential as acyl transferring agents and as a test case, we first performed the reaction of **2** with aniline in DMF solvent at ambient temperature. A slow reaction occurred to provide the expected acetanilide product in 40% yield after 24 h. However, to our delight the same reaction when heated at 70–80˚C produced quantitaive conversion in just 3 h to provide acetanilide in an isolated yield of 87%. Likewise, when benzoyl maleic hydrazide **3** was reacted with a slight excess of aniline in DMF (70–80˚C/2 h), benzanilide was formed in 92% yield. Of the other solvents examined, we found THF, Dioxan or CH_3CN to be less effective (*ca* 10–35% conversion to benzanilide over 24 h at 70–80˚C) than DMF solvent. Although, NMP solvent was as effective as DMF, being inexpensive we have preferred to use DMF in all acylation reactions.

After having established the potential of **2** and **3** as acyl transferring agents, we carried out acylations of various aromatic and aliphatic animes in order to assess the generality of the present procedure. Our results are collected in Table 1. The yields of the N-acylated products (entries 1–14) are fairly high and reactions are completed within 2–6 h of heating at 70–80ºC without the need for any catalyst. Acylation of *p*-amino with **2** occurred chemoselectively to give exclusively the N-acetyl derivative (entry 6) in high yield. 4-Nitroaniline, containing a relatively poor reacting amine also successfully participated in the acylation with **3** during 6 h of heating to afford the benzoyl product in 60% yield (entry 7). Interestingly, anthranilic acid, an amino acid also successfully participated in acylations with **2** and **3** giving N-acetyl and N-benzoyl products in 68 and 65%, respectively (entries 8 and 9).

Presumably on account of relatively poor nucleophilicities, phenols and alcohols failed to undergo acylation either with **2** or **3** under the conditions in which amines are acylated readily. However, acylations of phenols and alcohols could be successfully achieved in the presence of triethylamine as a base to afford good yields of the corresponding acylated products; a few representative examples are cited in Table 1 (entries 15–20). Thiophenol also reacted successfully with **3** in DMF/Et_3N condition to afford thiophenyl benzoate in 75% isolated yield.

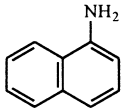
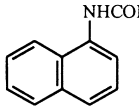
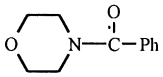
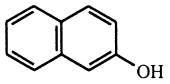
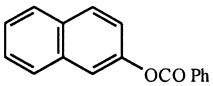
In conclusion, we have demonstrated high potential of acyl maleic hydrazides **2** and **3** in effecting the acylations of amines, phenols, alcohols and thiols in good to excellent yields under convenient and easy to execute experimental conditions. Furthermore, unlike many acylating agents known in the literature, compounds **2** and **3** are stable, easy to handle crystalline solids which should make them attractive acyl transfering agents in many applications.

Experimental

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu FTIR-

* To receive any correspondence. E-mail: sh_mashraqui@yahoo.com
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table1 Acylation[a] using **2** and **3**

Entry[b,c]	Substrate		Acylated product[c]	Time/h 70–80 °C	Yield[d]/%	m.p.(lit.)/°C
1	$PhNH_2$	**(4)**	PhNHCOMe	3	87	113 (114)[13]
2		**(4)**	PhNHCOPh	2	92	161 (163)[13]
3	4 -Me -$C_6H_4NH_2$	**(5)**	4 -Me- $C_6H_4NHCOMe$	3	90	154 (154)[13]
4		**(5)**	4-Me-$C_6H_4NHCOPh$	3	95	156 (158)[13]
5	4 -$ClC_6H_4NH_2$	**(6)**	4 -Cl $C_6H_4NHCOMe$	5	88	178 (179)[13]
6	4 -$HOC_6H_4NH_2$	**(7)**	4 -$HOC_6H_4NHCOPh$	4	72	234 (234)[13]
7	4 -$O_2NC_6H_4NH_2$	**(8)**	4 -$O_2NC_6H_4NHCOPh$	6	60	210 (211)[13]
8	4 -$HO_2CC_6H_4NH_2$	**(9)**	4 -$HO_2CC_6H_4NHCOMe$	4	68	249 (251)[13]
9		**(9)**	4 -$HO_2CC_6H_4NHCOPh$	3	65	274 (274)[13]
10		**(10)**		5	83	160 (161)[13]
11	$PhCH_2NH_2$	**(11)**	$PhCH_2NHCOPh$	6	86	105 (105)[14]
12	$PhCH_2CH_2NH_2$	**(12)**	$PhCH_2CH_2NHCOPh$	6	74	116 (116)[14]
13	$PhNH_2NH_2$	**(13)**	PhNHNHCOMe	2	65	126 (128)[13]
14		**(14)**		6	60	75 (75)[14]
15	PhOH	**(15)**	PhOCOMe	5	80	oil[e]
16		**(15)**	PhOCOPh	6	91	68 (69)[15]
17	4-Me-C_6H_4OH	**(16)**	4-Me-C_6H_4OCOPh	6	86	70 (71)[15]
18		**(17)**		5	95	105 (107)[15]
19	$PhCH_2OH$	**(18)**	$PhCH_2OCOPh$	6	69	oil[e]
20	CH_3OH	**(19)**	CH_3OCOPh	6	90	oil[e]
21	PhSH	**(20)**	PhSCOPh	6	78	oil[e]

[a]Acylations using either **2** or **3** were carried out on 5 mmol scale using a slight excess of substrates. [b]For entries **1–14**, reactions were done in DMF and for entries **15–21** triethylamine was added as a base catalyst. [c]Acetyl and benzoyl products are obtained on reactions with **2** and **3**, respectively. [d]Yeilds refer to TLC homogenous products. [e]Oily products characterised by superimpoable IR spectra with the authentic products.

4200 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian-VR (300 MHz) using TMS as an internal standard.

Preparation of mono-O-acetyl maleic hydrazide **2**: Maleic hydrazide 9.18 g (90 mmol) **1** was refluxed with of acetic anhydride (25cm^3) for 5 h. The reaction mixture was concentrated in vacuum rotatory evaporator and the residual solid crystallised from benzene to afford 9.7 g (75% yield) of **2**, m.p. 120–123°C (lit[16]. m.p. 122–123 °C); MS; *m/z* 155 (M+1); IR (KBr): 1765 and 1670 cm^{-1} ; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 2.28 (3H, s), 4.46 (1H, bs, D_2O exchangeable), 7.2–7.4 (2H, *J*=8Hz); ^{13}C NMR ($CDCl_3$) 170.37,163.32,-150.1,133.33,132.40,20.5

Preparation of mono-O-benzoyl maleic hydrazide **3**: Maleic hydrazide **1** was benzoylated as per the published procedure to afford **3** as a colourless solid in 70% yield, m.p. 160–162 °C (lit[17]., m.p. 162.5–164.5 °C).MS; *m/z* 217 (M+1); IR (KBr):1735 and 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$; 300 MHz); δ7.25-8.1(ArH and NH); ^{13}C NMR ($CDCl_3$): 164.35, 161.84, 148.35, 134.53, 132.54, 130.49, 128.81,127.72.

Typical procedure for N-acylation : *p*-Toluidine (0.642 g ; 5 mmol) and mono-acetyl maleic hydrazide **2** (0.062 g; 5 mmol) were heated together in DMF (5 ml) at 70–80 °C for 3h whereby TLC indicated completion of the reaction. The reaction was diluted with cold water and the precipitated solid filtered and washed sequencially with 5% HCl, saturated Na_2CO_3 solution and finally with water. Air drying of the crude product followed by crystallisation from aqueous alcohol gave acetanilide (entry 3, Table 1) m.p.154 °C (lit[13] 154 °C) in 92% yield.

Typical procedure for O-acylation : Phenol (0.564 g; 5 mmol) and benzoate **3** (1.08 g; 5 mmol) were dissolved in DMF (5 ml) containing 0.5 ml of $(C_2H_5)_3N$. The reaction was heated at 75–80°C for 5 h where by the reaction was judged to be complete by TLC analysis. The reaction mixture was worked up as described above and the crude product crystallised from aqueous alcohol to give colourless crystals of phenyl benzoate (entry 16,Table 1), m.p. 68 °C (lit[15]. m.p 69°C) in 77% yield.

We wish to thank Council of Scientific and Industrial Research, New Delhi, India for support of this work and Dr. Sukeerthi Kumar for helpful discussions.

Received 17 June 2002; accepted 19 September 2002
Paper 02/1424

References

1 (a) P.J. Kocienski., *Protective Groups*, Georg Thieme Verlag Stuttgart. New York, 1999; (b) T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2nd edn. Wiley, New York 1991; (c) D.P.N. Satchell, *Quart. Rev. (Lond.)* 1963, **16**, 160; (d) Haslam, *Tetrahedron*, 1980, **36**, 2409; Z.J.Kaminski, *Synthesis*, 1987, 917.
2 (a) E.F.V Scriven., *Chem. Soc. Rev*., 1983, **12**, 129; (b) W. Steglich and G. Holfe, *Angew.Chem. Int. Ed. Engl*., 1978, **17**, 569.
3 (a) R.C. Larock, *Comprehensive Organic Transformations*, VCH, New York, 1989 pp.981; (b) J. March, *Advanced Organic Chemistry*, pp.370 3rd edn. Wiley Easter Ltd, New Delhi.
4 (a) K.C. Nicolaou, *Tetrahedron*, 1977, **33**, 683; (b) S. Masamune, G.S. Bates and J.W. Corcoran, *Angew.Chem.Int.Ed.Engl*., 1977, **16**, 585.
5 M.J. Smith, J.G. Moffit and H.G. Khorana, *J.Am.Chem.Soc*., 1958, **80**, 6204.
6 T. Mukaiyama, *Angew.Chem.Int.Ed.Engl*.,1970, **18**, 70.
7 S. Staab, *Angew. Chem. Int. ed. Engl*. 1960, 351.
8 J. Zbigniew and Z.J. Kaminski, *Tetrahedron Lett*., 1985, **26**, 2901.
9 S. Ikegami, H. Uchiyama, H. Hayama, T. Katsuki, M. Yamaguchi, *Tetrahedron*, 1988, **44**, 5333.
10 D.L. Hughes, *Org. React.* 1992, **40**, 335.
11 (a) A.R. Katrittzky, B. Yand and D. Semenzin, *J.Org.Chem*., 1997, **62**, 726-728; (b) A.G.M. Barret, D.C. Braddock, *J.Chem.Soc., Chem. Commun*., 1997, **24**, 351; (c) K. Ishihara, M. Kubota and H. Yamamoto, *Synlett*, 1996, 265; (d) J. Izumi,

I. Shiina and T. Mukaiyama, *Chem. Lett*., 1995,141; (e) J. Iqbal and R.R. Srivastava, *J. Org. Chem*., 1992, **57**, 2001; (f). A.R. Katritzky, Hai-Ying He and K. Suzuki *J.Org.Chem*., 2000, **65**, 8210-8213; (g) M.Y. Lin and T.V. Rajan Babu, *Org. Lett*., 2000, **2**, 1000.

12. A.R.Karritzky and C.W.Rees, *Comprehensive Heterocyclic Chemistry,* Vol. **3**, p.4, Pergamon Press, New York 1984
13 A.I. Vogel, *Textbook of Practical Organic Chemistry*, p.1372 5th edn, Longman, London 1989.
14 A.I. Vogel, *Textbook of Practical Organic Chemistry,* p.1370, 5th edn, Longman, London, 1989.
15 A.I. Vogel, *Textbook of Practical Organic Chemistry,* p.1310, 5th edn, Longman, London, 1989.
16 H. Feuer and H. Rubinstein, *J.A.Chem.Soc*., 1958, **80**, 5873.
17 D. Stefyne and W.L. Howard *J.Org.Chem*., 1953, **19**, 115.