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Short communication

One-pot synthesis of highly functionalized stable ketenimines of 2,2,2-trifluoro-*N*-aryl-acetamides

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ABSTRACT

Three-component reaction of alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of 2,2,2-trifluoro-*N*-aryl-acetamides in dichloromethane at ambient temperature afforded dialkyl 2-(*N*-(aryl)-2,2,2-trifluoroacetamido)-3-(alkylimino) methylene-succinate derivatives in excellent yields.

1. Introduction

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity [1]. One of the ways to fulfill these goals is the development and use of multicomponent reactions which consist of several simultaneous bond-forming reactions and allow the high efficient synthesis of complex molecules starting from simple substrates in a one-pot manner [2–4]. In recent years, the synthetic applications of multifunctional heteroallenes have been widely investigated [5,6]. In spite of extensive developments in the chemistry of modified ketenes and isocyanates [7], little attention has been paid to the synthesis of ketenimines [8]. Ketenimines are important reactive intermediates that occur as transient compounds in many thermal and photochemical reactions [9–12]. There has been intense interest in their addition reactions, such as cycloaddition [13–15], nucleophilic [11,16,17], and electrophilic [18,19] addition. The trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylates and isocyanides with OH, NH, and CH acids has been widely studied [20–24]. In continuation of our works on the reaction between isocyanides and acetylenic esters in the presence of organic acids [25–28], in this paper we present the results of an extended investigation on the reactivity of the intermediate zwitterion with 2,2,2-trifluoro-*N*-aryl-acetamides as N–H acids in dichloromethane leading to the formation of thermally stable ketenimine derivatives in good yields. Alkyl isocyanides **1** and dialkyl acetylenedicarboxylates **2** in the presence of 2,2,2-trifluoro-*N*-aryl-acetamides **3** undergo a smooth 1:1:1 addition reaction in dichloromethane at ambient temperature to produce dialkyl 2-(*N*-(aryl)-2,2,2-trifluoroacetamido)-3-(alkylimino) methylene-succinate derivatives **4** in excellent yields (Scheme 1). Previously, we reported similar reaction between alkyl isocyanides, acetylene diesters and *N*-phenyl-acetamide to produce unsaturated amidines [25].

2. Results and discussion

The results on the synthesis of ketenimines are given in Table 1. The structures of compounds **4a–f** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The mass spectrum of **4a** displayed the molecular ion peak at m/z = 474 which is consistent with the formation of a 1:1:1 adduct of dimethyl acetylenedicarboxylate, cyclohexyl isocyanide, and *N*-(4-chlorophenyl)-2,2,2-trifluoroacetamide. The IR spectra of the ketenimines exhibit a strong absorption band at about 2030 cm^{-1}. The IR spectrum of **4a** exhibited the absorption band for the ketenimine moiety at 2060 cm^{-1}and for the ester carbonyl groups at 1747 and 1696 cm^{-1}.

The ^{1}H NMR spectrum of compound **4a** exhibited three sharp singlet signals readily recognized as arising from methoxy (δ = 3.65 and 3.77), and CH (δ = 5.59) protons. The N*CH* proton was appeared as a multiplet at 3.62 ppm and the signals related to methylene

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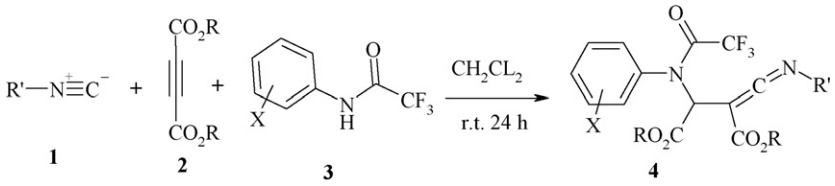


1 2 3 4

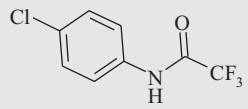
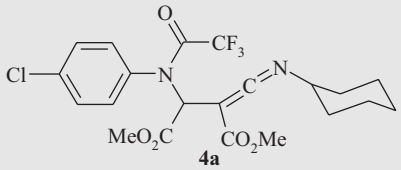
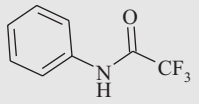
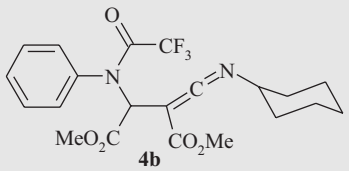
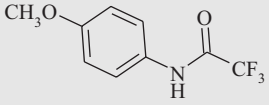
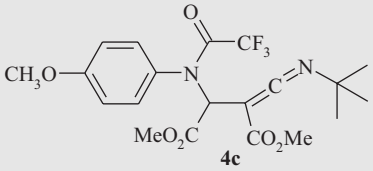
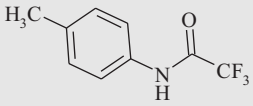
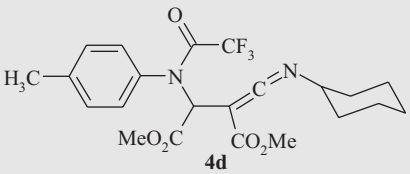
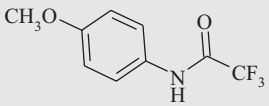
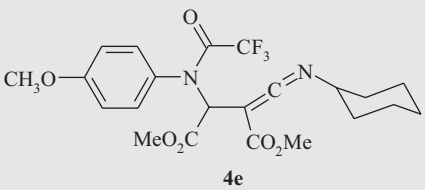
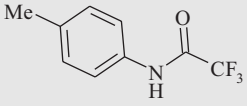
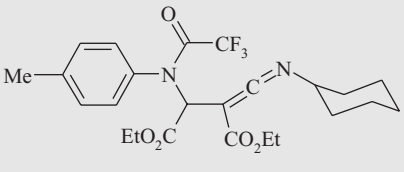
Scheme 1.

groups of cyclohexyl moiety were observed as multiplets at 1.27–1.82 ppm.

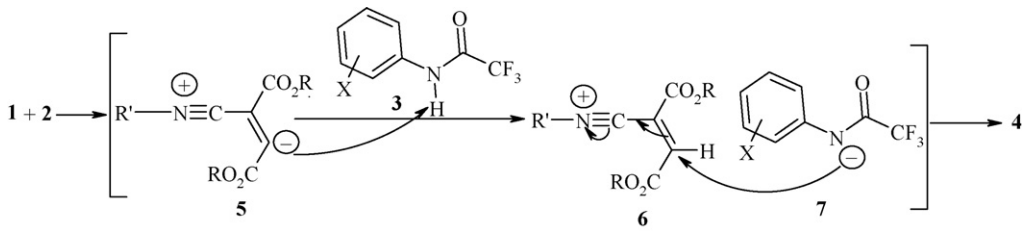
The protons of the aryl group exhibited characteristic signals in the aromatic region of the spectrum. The ^{13}C NMR spectrum of compound **4a** showed 19 distinct resonances in agreement with the proposed structure. The sp^2-hybridized carbon atom of the ketenimine residue appeared at $\delta = 60.8$ ppm, as a result of strong electron delocalization. Partial assignments of these resonances are given in Section 4.

Although we have not established the mechanism of the reaction between an isocyanide and an acetylenic ester in the presence of 2,2,2-trifluoro-*N*-phenyl-acetamide **3** experimentally,

Table 1
Synthesis of ketenimines.

Entry	Substrate	R′	R	Product	Yield[a] (%)
1		Cyclohexyl	Me	 **4a**	85
2		Cyclohexyl	Me	 **4b**	89
3		*tert*-Buty	Me	 **4c**	90
4		Cyclohexyl	Me	 **4d**	82
5		Cyclohexyl	Me	 **4e**	80
6		Cyclohexyl	Et	 **4f**	85

[a] Isolated yields.



Scheme 2.

a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides [29–33], it is reasonable to assume that the functionalized ketenimine **4** results from the initial addition of the isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct **5** by 2,2,2-trifluoro-*N*-phenyl-acetamide. Then, the positively charged ion **6** is attacked by anion **7** to give the product **4** (Scheme 2).

3. Conclusion

In conclusion, here we report a simple one-pot reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of 2,2,2-trifluoro-*N*-aryl-acetamides that provides access to stable ketenimine derivatives of potential synthetic interest. The present procedure has the advantage that not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.

4. Experimental

4.1. General

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a shimadzu IR-470 spectrometer. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at 500.13, 125.77 and 470.56 MHz, respectively. ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained on solution in $CDCl_3$ using TMS or $CFCl_3$ as internal standard. 2,2,2-Trifluoro-*N*-aryl-acetamides were prepared by treatment of anilines and trifluoroacetic acid in microwave [34]. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

4.2. Typical procedure for the preparation of 4a–f

To a magnetically stirred solution of dialkyl acetylenedicarboxylate (2 mmol) and 2,2,2-trifluoro-*N*-phenyl-acetamide (2 mmol) in CH_2Cl_2 (10 mL) was added a solution of alkyl isocyanide (2 mmol) in CH_2Cl_2 (5 mL) dropwise at r.t. over 10 min. The mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (silica gel, hexane–*EtOA*c, 5:1) to afford the pure title compounds.

4.3. Spectral data

4.3.1. Dimethyl 2-(N-(4-chlorophenyl)-2,2,2-trifluoroacetamido)-3-(cyclohexylimino) methylene-succinate (4a)

Yellow oil; yield 0.80 g (85%); IR (KBr) (ν_{max}, cm^{-1}): 2060 (N=C=C), 1747, 1696 (C=O, ester). Analyses: Calcd. for $C_{21}H_{22}ClF_3N_2O_5$: C, 53.12; H, 4.67; N, 5.90%. Found: C, 53.19; H, 4.57; N, 5.81%. MS (*m*/*z*, %): 474 (M^+, 4). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.27–1.82 (10 H, 5 CH_2 of cyclohexyl), 3.62 (1 H, m, CH of cyclohexyl), 3.65 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 5.59 (1 H, s, CH), 7.25–7.35 (4 H, aromatic) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.2, 24.2, 25.1, 33.4 and 33.5 (5 CH_2 of cyclohexyl), 52.2 (OCH_3), 53.7 (OCH_3), 57.6 (CH of cyclohexyl), 60.8 (N=C=*C*), 62.1 (CH), 118.2 (q, $^1J_{FC}$ = 285 H_Z, *C*F_3), 129.5, 129.7, 136.0 and 136.3 (C aromatic), 157.4 (q, $^2J_{FC}$ = 36 H_Z, *C*O*C*F_3),160.6 (N=*C*=C), 167.0 (*C*O_2Me), 169.8 (*C*O_2Me) ppm.

^{19}F NMR (470.56 MHz, $CDCl_3$) δ = −75.6 (CF_3) ppm.

4.3.2. Dimethyl 2-(2,2,2-trifluoro-N-phenylacetamido)-3-(cyclohexylimino) methylene-succinate (4b)

Yellow oil; yield 0.78 g (89%); IR (KBr) (ν_{max}, cm^{-1}): 2075 (N=C=C), 1745, 1702 (C=O, ester). Analyses: Calcd. for $C_{21}H_{23}F_3N_2O_5$: C, 57.27; H, 5.26; N, 6.36%. Found: C, 57.36; H, 5.22; N, 6.39%. MS (*m*/*z*, %): 440 (M^+, 9). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.21–1.77 (10 H, 5 CH_2 of cyclohexyl), 3.58 (1 H, m, CH of cyclohexyl), 3.61 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 5.61 (1 H, s, CH), 7.25–7.34 (5 H, aromatic) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.0, 23.1, 25.4, 33.3 and 33.4 (5 CH_2 of cyclohexyl), 52.1 (OCH_3), 53.3 (OCH_3), 57.9 (CH of cyclohexyl), 60.7 (N=C=*C*), 62.1 (CH), 117.6 (q, $^1J_{FC}$ = 286 H_Z, *C*F_3), 128.9, 129.6, 130.0 and 137.8 (C aromatic), 157.5 (q, $^2J_{FC}$ = 36 H_Z, *C*O*C*F_3), 161.4 (N=*C*=C), 168.7 (*C*O_2Me), 169.8 (*C*O_2Me) ppm.

^{19}F NMR (470.56 MHz, $CDCl_3$) δ = −75.6 (CF_3) ppm.

4.3.3. Dimethyl 2-(2,2,2-trifluoro-N-(4-methoxyphenyl)acetamido)-3-(tert-butylimino) methylene-succinate (4c)

Yellow oil; yield 0.79 g (90%); IR (KBr) (ν_{max}, cm^{-1}): 2070 (N=C=C), 1745, 1696 (C=O, ester). Analyses: Calcd. for $C_{20}H_{23}F_3N_2O_6$: C, 54.05; H, 5.22; N, 6.30%. Found: C, 54.12; H, 5.26; N, 6.27%. MS (*m*/*z*, %): 444 (M^+, 9). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.30 (9 H, s, CMe_3), 3.37 (3 H, s, OCH_3), 3.71 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 5.53 (1 H, s, CH), 6.96–7.49 (4 H, aromatic) ppm. ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 30.6 (*CMe*$_3$), 52.1 (OCH_3), 52.2 (OCH_3), 52.6 (OCH_3), 53.3 (*C*Me_3), 57.2 (N=C=*C*), 62.6 (CH), 118.3 (q, $^1J_{FC}$ = 287 H_Z, *C*F_3), 129.7, 130.0, 135.3 and 139.8 (C aromatic), 157.5 (q, $^2J_{FC}$ = 36 H_Z, *C*O*C*F_3), 161.8 (N=*C*=C), 168.9 (*C*O_2Me), 171.2 (*C*O_2Me) ppm.

^{19}F NMR (470.56 MHz, $CDCl_3$) δ = −75.6 (CF_3) ppm.

4.3.4. Dimethyl 2-(2,2,2-trifluoro-N-p-tolylacetamido)-3-(cyclohexylimino) methylene-succinate (4d)

Yellow oil; yield 0.74 g (82%); IR (KBr) (ν_{max}, cm^{-1}): 2075 (N=C=C), 1744, 1699 (C=O, ester). Analyses: Calcd. for $C_{22}H_{25}F_3N_2O_5$: C, 58.15; H, 5.54; N, 6.16%. Found: C, 58.06; H, 5.63; N, 6.21%.. MS (*m*/*z*, %): 454 (M^+, 5). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.20–1.84 (10 H, 5 CH_2 of cyclohexyl), 2.37 (3 H, s, CH_3), 3.68 (3 H, s, OCH_3), 3.74 (1 H, m, CH of cyclohexyl), 3.81 (3 H, s, OCH_3), 5.60 (1 H, s, CH), 6.95–7.48 (4 H, aromatic) ppm. ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 21.3 (*C*H_3), 24.3, 24.8, 26.1, 33.3 and 33.4 (5 CH_2 of cyclohexyl), 52.2 (OCH_3), 53.3 (OCH_3), 58.1 (CH of cyclohexyl), 60.8 (N=C=*C*), 62.1 (CH), 117.2 (q, $^1J_{FC}$ = 285 H_Z, *C*F_3), 129.8, 130.2, 136.5 and 139.8 (C aromatic), 156.86 (q, $^2J_{FC}$ = 36 H_Z, *C*O*C*F_3), 164.4 (N=C=C), 169.1 (*C*O_2Me), 169.9 (*C*O_2Me) ppm.

^{19}F NMR (470.56 MHz, $CDCl_3$) δ = −75.5 (CF_3) ppm.

*4.3.5. 4.3.5.Dimethyl 2-(2,2,2-trifluoro-N-(4-methoxyphenyl)acetamido)-3-(cyclohexylimino) methylene-succinate (**4e**)*

Yellow oil; yield 0.75 g (80%); IR (KBr) (ν_{max}, cm^{-1}): 2055 (N=C=C), 1741, 1702 (C=O, ester). Analyses: Calcd. for $C_{22}H_{25}F_3N_2O_6$: C, 56.17; H, 5.36; N, 5.95%. Found: C, 56.24; H, 5.32; N, 5.83%.. MS (*m/z*, %): 470 (M^+, 4). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.21–1.78 (10 H, 5 CH_2 of cyclohexyl), 3.62 (1 H, m, CH of cyclohexyl), 3.37 (3 H, s, OCH_3), 3.70 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 5.63 (1 H, s, CH), 7.25–7.35 (4 H, aromatic) ppm. ^{13}C NMR (125.7 MH_Z, $CDCl_3$): δ = 23.1, 24.2, 25.2, 33.3 and 33.4 (5 CH_2 of cyclohexyl), 52.2 (OCH_3), 53.0 (OCH_3), 53.4 (OCH_3), 57.2 (CH of cyclohexyl), 60.9 (N=C=*C*), 62.3 (CH), 118.2 (q, $^1J_{FC}$ = 286 H_Z, *C*F_3) 128.9, 130.3, 133.5 and 137.8 (C aromatic), 157.2 (q, $^2J_{FC}$ = 36 H_Z, *C*OCF_3), 160.59 (N=*C*=C), 169.81 (*C*O_2Me), 171.28 (*C*O_2Me) ppm.

^{19}F NMR (470.56 MHz, $CDCl_3$) δ = −75.6 (CF_3) ppm.

*4.3.6. Diethyl 2-(2,2,2-trifluoro-N-p-tolylacetamido)-3-(cyclohexylimino) methylene-succinate (**4f**)*

Yellow oil; yield 0.82 g (85%); IR (KBr) (ν_{max}, cm^{-1}): 2070 (N=C=C), 1745, 1693 (C=O, ester). Analyses: Calcd. for $C_{24}H_{29}F_3N_2O_5$: C, 59.74; H, 6.06; N, 5.81%. Found: C, 59.71; H, 6.12; N, 5.74%. MS (*m/z*, %): 482 (M^+, 11). ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.23 (3 H, t, $^3J_{HH}$ = 7 H_Z, OCH_2CH_3), 1.32 (3 H, t, $^3J_{HH}$ = 7 H_Z OCH_2CH_3), 1.27–2.01 (10 H, 5 CH_2 of cyclohexyl), 2.37 (3 H, s, CH_3), 3.76 (1 H, m, CH of cyclohexyl), 4.13 (2 H, q, $^3J_{HH}$ = 7 H_Z, OCH_2CH_3), 4.26 (2 H, q, $^3J_{HH}$ = 7 H_Z, OCH_2CH_3), 5.58 (1 H, s, CH), 7.06–7.48 (4 H, aromatic) ppm. ^{13}C NMR (125.7MH_Z, $CDCl_3$): δ = 14.7, 14.5 (2 OCH_2CH_3), 21.6 (CH_3), 24.1, 24.2, 25.5, 33.3 and 33.4 (5 CH_2 of cyclohexyl), 58.7 (CH of cyclohexyl), 60.7 (N=C=*C*), 60.9 (CH), 62.3, 62.5 (2 OCH_2CH_3), 118.34 (q, $^1J_{FC}$ = 286 H_Z, *C*F_3), 120.9, 129.8, 130.1, and 139.7 (aromatic), 156.9 (q, $^2J_{FC}$ = 36 H_Z, *C*OCF_3), 165.8 (N=*C*=C), 168.5 (*C*O_2Me), 169.5 (*C*O_2Me) ppm.

^{19}F NMR (470.56 MHz, $CDCl_3$) δ = −75.5 (CF_3) ppm.

References

[1] B.M. Trost, Science 254 (1991) 1471–1477.
[2] H. Bienayme, C. Hulme, G. Oddon, P. Schmidt, Chem. Eur. J. 6 (2000) 3321–3329.
[3] A.J. Von Wangelin, H. Neumann, D. Gördes, S. Klaus, D. Strübing, M. Beller, Chem. Eur. J. 9 (2003) 4286–4294.
[4] R.V.A. Orru, M. de Greef, Synthesis (2003) 1471–1499.
[5] W. Reichen, Chem. Rev. 78 (1978) 569–588.
[6] J. Motoyoshiya, A. Teranishi, R. Mikoshiba, I. Yamamoto, H.C. Gotoh, J. Org. Chem. 45 (1980) 5385–5387.
[7] M. Ishida, T. Minami, T. Agawa, J. Org. Chem. 44 (1979) 2067–2073.
[8] G. Krow, Angew. Chem. Int. Ed. Eng. 10 (1971) 435–449.
[9] T.T. Tidwell, Ketenes, Wiley, New York, 1995.
[10] M.W. Barker, W.E. McHenry, The Chemistry of Ketenes, Allenes and Related Compounds, Part 2, Wiley, New York, 1980.
[11] T.T. Tidwell, Acc. Chem. Res. 23 (1990) 273–279.
[12] Y. Chiang, A.S. Grant, H.-X. Guo, A.J. Kresge, S.W. Paine, J. Org. Chem. 62 (1997) 5363–5370.
[13] M. Schmittel, J.P. Steffen, M.A.W. Angel, B. Engels, C. Lennartz, M. Hanrath, Angew. Chem. Int. Ed. 37 (1998) 1562–1564.
[14] M. Alajarin, A. Vidal, F. Tovar, M.C.R. Arellano, Tetrahedron Asymmetry 15 (2004) 489–494.
[15] M.H. Mosslemin, I. Yavari, M. Anary-Abbasinejad, M.R. Nateghi, J. Fluorine Chem. 125 (2004) 1497–1500.
[16] G.G.H. Qiao, J. Andraos, C. Wentrup, J. Am. Chem. Soc. 118 (1996) 5634–5638.
[17] K. Sung, T.T. Tidwell, J. Am. Chem. Soc. 120 (1998) 3043–3048.
[18] C. Fromont, S. Masson, Tetrahedron 55 (1999) 5405–5418.
[19] N. Pietri, T. Chiavassa, A. Allouche, J.P. Aycard, J. Phys. Chem. A 101 (1997) 1093–1098.
[20] A. Shaabani, E. Soleimani, H.R. Khavasi, R.D. Hoffmann, U.C. Rodewald, R. Pöttgen, Tetrahedron Lett. 47 (2006) 5493–5496.
[21] I. Yavari, M. Anary-Abbasinejad, A. Alizadeh, Z. Hossaini, Tetrahedron 59 (2003) 1289–1292.
[22] I. Yavari, H. Zare, B. Mohtat, Mol. Diversity 10 (2006) 247–250.
[23] I. Yavari, A. Alizadeh, M. Anary-Abbasinejad, H.R. Bijanzadeh, Tetrahedron 59 (2003) 6083–6086.
[24] A. Shaabani, M.B. Teimouri, S. Arab-Ameri, Tetrahedron Lett. 45 (2004) 8409–8413.
[25] M. Anary-Abbasinejad, M.H. Mosslemin, S. Tahan, H. Anaraki-Ardakani, J. Chem. Res. 3 (2006) 170–172.
[26] M. Anary-Abbasinejad, M.H. Mosslemin, H. Anaraki-Ardakani, S. Tahan, J. Chem. Res. 5 (2006) 306–308.
[27] M. Anary-Abbasinejad, H. Anaraky-Ardakani, F. Rastegari, A. Hassanabadi, J. Chem. Res. 10 (2007) 602–604.
[28] M. Anary-Abbasinejad, H. Anaraki-Ardakani, F. Ghanea, Monatsh. Chem. (2009), doi:10.1007/s00706-008-0039-9.
[29] I. Ugi, Angew. Chem. Int. Ed. Eng. 21 (1982) 810–812.
[30] A. Dömling, Chem. Rev. 106 (2006) 17–89.
[31] H.M. Walborsky, M.P. Periasamy, in: C. Suppl, S. Patai, Z. Rappoport (Eds.), The Chemistry of Functional Groups, Wiley, New York, 1983 , p. 835 (Chapter 20).
[32] S. Marcaccini, T. Torroba, Org. Prep. Proced. Int. 25 (1993) 141–143.
[33] V. Nair, A.U. Viond, J.S. Nair, A.R. Sreekanth, N.P. Rath, Tetrahedron Lett. 41 (2000) 6675–6679.
[34] J. Salazar, S.E. López, O. Rebollo, J. Fluorine Chem. 124 (2003) 111–113.