Journal of Fluorine Chemistry 130 (2009) 591–594

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Short communication

Synthesis of α-trifluoromethylstyrene derivatives *via* Ni-catalyzed cross-coupling of 2-bromo-3,3,3-trifluoropropene and aryl Grignard reagents

Osamu Kobayashi, Daisuke Uraguchi [1], Tetsu Yamakawa *

Sagami Chemical Research Center, Hayakawa 2743-1, Ayase, Kanagawa 252-1193, Japan

ARTICLE INFO

Article history:
Received 14 January 2009
Received in revised form 4 March 2009
Accepted 5 March 2009
Available online 20 March 2009

Keywords:
α-Trifluoromethylstyrene
2-Bromo-3,3,3-trifluoropropene
Aryl Grignard reagents
Nickel catalyst
Cross-coupling

ABSTRACT

The Ni-catalyzed cross-coupling of 2-bromo-3,3,3-trifluoropropene and aryl Grignard reagents was investigated. When $NiCl_2(PPh_3)_2$ was used as a catalyst, the highest yield of α-trifluoromethylstyrene (89%) from 2-bromo-3,3,3-trifluoropropene and PhMgBr was obtained in 1,3-dimethyl-2-imidazolidinone at 50 °C for 30 min. Various α-trifluoromethylstyrene derivatives could be produced in satisfactory yields by $NiCl_2(PPh_3)_2$-catalyzed coupling using aryl Grignard reagents.

1. Introduction

α-Trifluoromethylstyrene derivatives have attracted considerable attention because they are industrially important compounds in the fields of medicinal, agricultural and material sciences [1]. With regard to the metal-catalyzed coupling for their synthesis, the Pd-catalyzed coupling of zinc or boronic acid reagents derived from 2-bromo-3,3,3-trifluoropropene (BTP) with aryl halides [2] and BTP with arylboronic acid [3] have been reported thus far. Recently, we carried out the Pd-catalyzed coupling of BTP and arylmagnesium bromides (ArMgBr) in order to demonstrate the use of more environmentally benign reagent [4]. It is well known that nickel compounds catalyze cross-coupling of vinyl halides and ArMgBr [5]. Therefore, more economical process for α-trifluoromethylstyrene derivatives synthesis using nickel catalysts will be developed.

In the Pd-catalyzed coupling of BTP and ArMgBr, C–F bonds in BTP were intact [4] as well as the other Pd-catalyzed coupling [2,3]. In addition, by-products, which are formed by the reaction of α-trifluoromethylstyrene and phenylmagnesium bromide (PhMgBr) [6], were not detected by GC and ^{19}F NMR at all. On the other hand, the combination of Ni catalysts and Grignard reagents are known to cleave frequently C–F bonds in alkyl fluorides [7]. Therefore, the appropriate conditions for the suppression of C–F bond cleavage of the desired products and/or BTP should be developed for realizing requisite Ni-catalyzed coupling of BTP.

In this study, we investigated the synthesis of α-trifluoromethylstyrene derivatives by the use of the Ni-catalyzed coupling of BTP and ArMgBr. We found that $NiCl_2(PPh_3)_2$ efficiently catalyzed the synthesis of α-trifluoromethylstyrene derivatives in satisfactory yields without any by-products formed through C–F bond cleavage.

2. Results and discussion

First, we used one of the conventional Ni(II)-phosphine complexes, $NiCl_2(PPh_3)_2$, as a catalyst in the coupling of BTP and PhMgBr; PhMgBr is mainly responsible for the reduction of Ni(II) to Ni(0). Table 1 shows the yields of α-trifluoromethylstyrene by the use of various solvents under the condition that $NiCl_2(PPh_3)_2$ is 1.0 mol% of BTP (0.01 mmol) and the addition rate of THF solution of PhMgBr is 50 μL/min. α-Trifluoromethylstyrene was detected by GC and ^{19}F NMR in any solvents. It should be mentioned that by-products formed by the cleavage of C–F bonds of α-trifluoromethylstyrene [6] were not detected [4]. Polar and basic solvents (NMP, DMPU and DMI) gave the higher yields (entries 5–7) than the other solvents commonly used in Grignard reactions (entries 1–3) and 1,4-dioxane (entry 4) in which the Pd-catalyzed coupling occurred exclusively [4]. Particularly, the use of DMI resulted in satisfactory yield (entry 7).

---

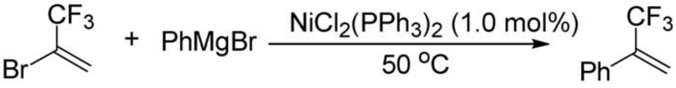
* Corresponding author. Tel.: +81 467769268; fax: +81 467774113.
E-mail address: t_yamakawa@sagami.or.jp (T. Yamakawa).

[1] Present address: Nagoya University, Graduate School of Engineering, Department of Applied Chemistry, Furo-cho, Chikusa-ku, Nagoya, Aichi 464-8603, Japan.

0022-1139/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2009.03.002

Table 1

$NiCl_2(PPh_3)_2$-catalyzed coupling of BTP and PhMgBr in various solvents.[a]



.

Entry	Solvent	GC yield (%)
1	THF	21
2	1,4-Dioxane	21
3	Diethylether	12
4	DME[b]	18
5	DMPU[c]	43
6	NMP[d]	44
7	DMI[e]	85

[a] $NiCl_2(PPh_3)_2$ 0.01 mmol, BTP 1.0 mmol, THF solution of PhMgBr (*ca.* 1.1 mol/L) 1.3 mL, addition rate of THF solution of PhMgBr 50 μL/min, solvent 1.0 mL, 50 °C, Ar atmosphere.

[b] 1,2-Dimethoxyethane.

[c] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

[d] *N*-Methyl-2-pyrrolidone.

[e] 1,3-Dimethyl-2-imidazolidinone.

Table 3

The coupling of BTP and PhMgBr using various Ni(II) compounds and phosphines.[a].

Entry	Ni(II) compound	Phosphine[b]	GC yield (%)
1	$Ni(acac)_2$	PPh_3	74
2	$Ni(acac)_2$	P(*p*-tolyl)$_3$	67
3	$Ni(acac)_2$	P(4-fluorophenyl)$_3$	74
4	$Ni(acac)_2$	P(*o*-tolyl)$_3$	48
5	$Ni(acac)_2$	dppm	8
6	$Ni(acac)_2$	dppe	5
7	$Ni(acac)_2$	dppp	55
8	$Ni(acac)_2$	dppb	64
9	$Ni(acac)_2$	dppf	7
10	$NiCl_2$(dppm)	–	49
11	$NiCl_2$(dppe)	–	40
12	$NiCl_2$(dppp)	–	66
13	$NiCl_2$(dppb)	–	65
14	$NiCl_2$(dppf)	–	14

[a] Ni(II) compound 0.01 mmol, [P]/[Ni] = 2, BTP 1.0 mmol, THF solution of PhMgBr (*ca.* 1.1 mol/L) 1.3 mL, addition rate of THF solution of PhMgBr 50 μL/min, DMI 1.0 mL, 50 °C, Ar atmosphere.

[b] dppm bis(diphenylphosphino)methane, dppe 1,2-bis(diphenylphosphino)ethane, dppp 1,3-bis(diphenylphosphino)propane, dppb 1,4-bis(diphenylphosphino)butane, dppf 1,1′-bis(diphenylphosphino)ferrocene.

Next, we examined the dependence of the addition rate and the loaded amount of $NiCl_2(PPh_3)_2$ on yield. The results are shown in Table 2. The yield gradually increased with the addition rate (entries 1–3) and reached 85% at 50 μL/min. In the range of 50–120 μL/min (entries 4–7), the yields were approximately constant. Since it is generally accepted that slow addition of a metallic reagent suppresses side reactions [8], we selected 50 μL/min in the reactions hereinafter. Actually, any by-products formed by abstraction of fluorine from α-trifluoromethylstyrene and BTP were not detected at all and the formed amounts of biphenyl were 3–5% in all entries. The low yields in entries 1–3 are possibly due to the small ratios of [PhMgBr]/[Ni]. The yields with various loaded amount of $NiCl_2(PPh_3)_2$ after the optimization of the addition rate are listed in entries 8–10. 0.5 mol% and 0.25 mol% of $NiCl_2(PPh_3)_2$ afforded remarkably low yields (entries 8 and 9). Since 5.0 mol% of $NiCl_2(PPh_3)_2$ provided 85% yield (entry 10), 1.0 mol% of the catalyst is enough for the satisfactory yield.

Under the conditions thus optimized, various Ni(II) compounds and phosphines were examined for the coupling of BTP and PhMgBr in DMI (Table 3). The yield obtained using the combination of $Ni(acac)_2$ and PPh_3 (entry 1) was somewhat lower than that using $NiCl_2(PPh_3)_2$ (85%, entry 6 in Table 1). The yield was independent of the electronic nature of the substituents on the phenyl rings in triarylphosphines (entries 2 and 3), while it decreased probably due to the steric hindrance of the substituent at the *ortho* position (entry 4). With the exception of dppp and dppb, the bidentate phosphine ligands were less effective than monodentate ligands in the coupling (entries 5, 6 and 9). Particularly, the remarkably low yield obtained with dppm is in contrast to the findings that dppm is exclusively efficient in the Pd-catalyzed coupling of BTP and PhMgBr [4]. The combination of $Ni(acac)_2$ and dppp or dppb gave moderate yields (entries 7 and 8) as well as $NiCl_2$(dppp) and $NiCl_2$(dppb) (entries 12 and 13). The other Ni(II) bidentate phosphine complexes were more active than the combination of $Ni(acac)_2$ and the corresponding bidentate phosphines, though the yields were less than 50% (entries 10, 11 and 14).

Table 2

$NiCl_2(PPh_3)_2$-catalyzed coupling of BTP and PhMgBr with various loaded amount of Ni and at various addition rate.[a].

Entry	$NiCl_2(PPh_3)_2$ (mol% of BTP)	Addition rate of PhMgBr solution (μL/min)	GC yield (%)
1	1.0	15	64
2	1.0	25	72
3	1.0	40	81
4	1.0	50	85
5	1.0	80	89
7	1.0	120	85
8	0.5	40	6
9	0.25	40	Trace
10	5.0	160	85

[a] BTP 1.0 mmol, THF solution of PhMgBr (*ca.* 1.1 mol/L) 1.3 mL, solvent 1.0 mL, 50 °C, Ar atmosphere.

Table 4 lists the results of the coupling using $NiCl_2(PPh_3)_2$ and various ArMgBr. Considering the practical use, the reaction scale was raised up to 10 times of that in Table 1. The optimized addition rate of the THF solution of PhMgBr was 200 μL/min, giving 89% yield of α-trifluoromethylstyrene. The moderate to satisfactory yields were obtained for each substrates. The fluorine or the chlorine substituent in 4-fluorophenylmagnesium bromide or 4-chlorophenylmagnesium bromide remained unreacted. This result indicates that not only C–F bond in BTP but also C–F or C–Cl bonds on the phenyl ring of the aryl Grignard reagents are not cleaved by this Ni catalyst under the given conditions [9]. This high selectivity as well as that the yield was not affected by the electronic nature of the substituents (entries 3–5) will represent a direct method for the synthesis of functionally substituted α-trifluoromethylstyrene derivatives from BTP.

In summary, we demonstrated the Ni-catalyzed coupling of BTP and ArMgBr. α-Trifluoromethylstyrene was obtained by the use of the versatile Ni(II) complex, $NiCl_2(PPh_3)_2$, in a satisfactory yield. This Ni(II) complex exhibited the high tolerance to the substituent in the reactions with various ArMgBr. The present method will provide more versatile and economical synthesis of α-trifluoromethylstyrene derivatives than the Pd-catalyzed coupling reported previously [4].

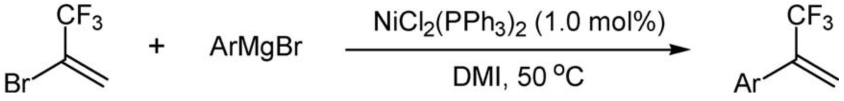
3. Experimental

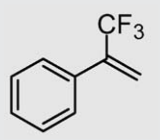
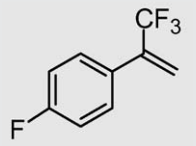
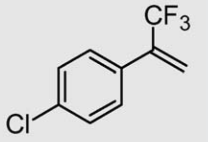
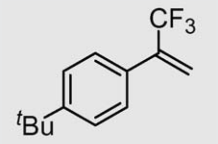
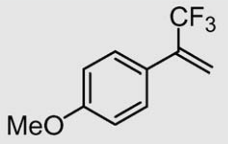
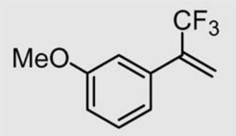
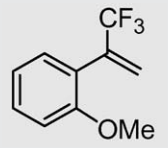
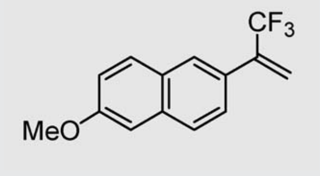
3.1. General experimental procedures

^1H and ^{19}F NMR spectra were recorded in $CDCl_3$ on Bruker DRX-500 (^1H 500 MHz) and DRX-250 (^{19}F 235 MHz) spectrometers using tetramethylsilane for ^1H NMR as an internal reference and fluorotrichloromethane for ^{19}F NMR as an external reference. Chemical shifts are expressed in ppm (δ). Multiplicities are indicated by s (singlet), d (doublet), dd (doublet of doublet), q (quartet), m (multiplet) and brs (broad singlet). Developed chromatograms were visualized by UV light. Flash chromatogra-

Table 4

$NiCl_2(PPh_3)_2$-catalyzed coupling of BTP and various aryl Grignard reagents.[a]



Entry	Ar	Product	Isolated yield (%)
1	Phenyl		89
2	4-Fluorophenyl		77
3	4-Chlorophenyl		70
4	4-*tert*-Butylphenyl		70
5	4-Methoxyphenyl		85
6	3-Methoxyphenyl		75
7	2-Methoxyphenyl		55
8	6-Methoxynaphthyl		64

[a] $NiCl_2(PPh_3)_2$ 0.1 mmol, BTP 10 mmol, THF solution of ArMgBr (*ca.* 1.1 mol/L) 13 mL, addition rate of THF solution of ArMgBr 200 μL/min, DMI 10 mL, 50 °C, Ar atmosphere.

phy was performed on silica gel (Kanto Chemical Co., N60). All commercially available reagents were used without further purification.

All reactions were carried out in flame-dried glassware under an Ar atmosphere. To a solvent containing a nickel compound (1.0 mol% of BTP), a phosphine ([P]/[Ni] = 2) and BTP, THF solution of an ArMgBr (*ca.* 1.1 mol/L, [ArMgBr]/[BTP] = *ca.* 1.4) was added at 50 °C using a syringe pump. The reaction mixture was then stirred for 30 min at the same temperature. After cooling to room temperature, an aliquot of the reaction mixture was diluted with pentane and the resulting solution was subjected to quantitative analyses by GC and ^{19}F NMR. Tridecane and 2,2,2-trifluoroethanol were used as internal standards for GC and ^{19}F NMR, respectively. The reaction mixture was passed through a silica gel column, and the eluted solution was concentrated in vacuo or distilled to isolate the desired products. All yields were calculated on the basis of the initial concentration of BTP.

3.2. Characterization of products

All products are known compounds. The full characterization of these compounds are shown in our previus report [4] and the references therein.

3.2.1. α-Trifluoromethylstyrene

^{1}H NMR (CDCl$_3$) δ: 7.47–7.43 (m, 2H), 7.40–7.35 (m, 3H), 5.95 (q, J_{HF} = 1.4 Hz, 1H), 5.76 (q, J_{HF} = 1.4 Hz, 1H). ^{19}F NMR (CDCl$_3$) δ: −65.1. MS (*m*/*z*): 172 $[M]^+$.

3.2.2. 4-Methoxy-1-(trifluoromethyl)vinylbenzene

^{1}H NMR (CDCl$_3$) δ: 7.39 (d, J_{HH} = 8.7 Hz, 2H), 6.90 (d, J_{HH} = 8.7 Hz, 2H), 5.86 (q, J_{HF} = 1.3 Hz, 1H), 5.69 (q, J_{HF} = 1.7 Hz, 1H), 3.83 (s, 3H). ^{19}F NMR (CDCl$_3$) δ: −65.1. MS (*m*/*z*): 202 $[M]^+$.

3.2.3. 3-Methoxy-1-(trifluoromethyl)vinylbenzene

^{1}H NMR (CDCl$_3$) δ: 7.32–7.27 (m, 1H), 7.05–7.02 (m, 1H), 6.98 (brs, 1H), 6.94–6.91 (m, 1H), 5.95 (q, J_{HF} = 1.3 Hz, 1H), 5.77 (q, J_{HF} = 1.6 Hz, 1H), 3.82 (s, 3H). ^{19}F NMR (CDCl$_3$) δ: −65.1. MS (*m*/*z*): 202 $[M]^+$.

3.2.4. 2-Methoxy-1-(trifluoromethyl)vinylbenzene

^{1}H NMR (CDCl$_3$) δ: 7.36–7.32 (m, 1H), 7.23–7.20 (m, 1H), 6.98–6.92 (m, 2H), 6.07 (d, J_{HF} = 1.4 Hz, 1H), 5.64 (d, J_{HF} = 1.0 Hz, 1H), 3.82 (s, 3H). ^{19}F NMR (CDCl$_3$) δ: −65.9. MS (*m*/*z*): 202 $[M]^+$.

3.2.5. 4-Tert-butyl-1-(trifluoromethyl)vinylbenzene

^{1}H NMR (CDCl$_3$) δ: 7.40 (brs, 4H), 5.91 (q, J_{HF} = 1.3 Hz, 1H), 5.75 (q, J_{HF} = 1.7 Hz, 1H), 1.33 (s, 9H). ^{19}F NMR (CDCl$_3$) δ: −65.1. MS (*m*/*z*): 228 $[M]^+$.

3.2.6. 4-Fluoro-1-(trifluoromethyl)vinylbenzene

^{1}H NMR (CDCl$_3$) δ: 7.42 (dd, J_{HH} = 8.7 Hz, J_{HF} = 5.3 Hz, 2H), 7.06 (dd, J_{HH} = 8.7 Hz, J_{HF} = 8.7 Hz, 2H), 5.94 (d, J_{HF} = 1.3 Hz, 1H), 5.71 (d, J_{HF} = 1.7 Hz, 1H). ^{19}F NMR (CDCl$_3$) δ: −112.8, −65.4. MS (*m*/*z*): 190 $[M]^+$.

3.2.7. 4-Chloro-1-(trifluoromethyl)vinylbenzene

^{1}H NMR (CDCl$_3$) δ: 7.41–7.34 (m, 4H), 5.97 (q, J_{HF} = 1.3 Hz, 1H), 5.76 (q, J_{HF} = 1.6 Hz, 1H). ^{19}F NMR (CDCl$_3$) δ: −65.2. MS (*m*/*z*): 206 $[M]^+$.

3.2.8. 6-Methoxy-2-[1-(trifluoromethyl)vinyl]naphthalene

^{1}H NMR (CDCl$_3$) δ: 7.86 (s, 1H), 7.76–7.71 (m, 2H), 7.54–7.50 (m, 1H), 7.19–7.15 (m, 1H), 7.14–7.11 (m, 1H), 5.99 (d, J_{HF} = 1.2 Hz, 1H), 5.86 (d, J_{HF} = 1.6 Hz, 1H), 3.92 (s, 3H). ^{19}F NMR (CDCl$_3$) δ: −64.6. MS (*m*/*z*): 252 $[M]^+$.

Acknowledgement

We are grateful to Tosoh F-Tech Co., Ltd. for providing BTP.

References

[1] A. Thompson, E.G. Corely, M.F. Huntington, E.J.J. Grabowski, J.F. Remenar, D.B. Collum, J. Am. Chem. Soc. 120 (1998) 2028–2038;
L. Tan, C.Y. Chen, R.D. Tillyer, E.J.J. Grabowski, P.J. Reider, Angew. Chem. Int. Ed. 38 (1999) 711–713;
S. Kishimura, M. Endo, M. Sasago, M. Shirai, M. Kadooka, Kokai Tokkyo Koho JP2002-311588.;
R.D. Allen, P.J. Brock, H. Ito, G.N. Wallraff, US Patent 0 164 538 (2002).

[2] B. Jiang, Y. Xu, J. Org. Chem. 56 (1991) 7336–7340;
B. Jiang, Q. Wang, C. Yang, M. Xu, Tetrahedron Lett. 42 (2001) 4083–4085.

[3] R.Q. Pan, X.-X. Liu, M.Z. Deng, J. Fluorine Chem. 95 (1999) 167–170;
K. Matoba, T. Mizukoshi, Y. Moriyama, PCT Int. Appl. WO200709431.

[4] O. Kobayashi, D. Uraguchi, T. Yamakawa, J. Mol. Catal. A: Chem. 302 (2009) 7–10.

[5] K. Tamao, K. Sumitani, M. Kumada, J. Am. Chem. Soc. 94 (1972) 4374–4376;
R.J.P. Corriu, J.P. Masse, J. Chem. Soc., Chem. Commun. (1972) 144.

[6] H. Ito, A.F. Renaldo, M. Ueda, Macromolecules 22 (1989) 45–51.

[7] J. Terao, A. Ikumi, H. Kuniyasu, N. Kambe, J. Am. Chem. Soc. 125 (2003) 5646–5647;
J. Terao, H. Toda, H. Watanabe, A. Ikumi, N. Kambe, Angew. Chem. Int. Ed. 43 (2004) 6180–6182;
J. Terao, H. Watanabe, N. Kambe, J. Am. Chem. Soc. 127 (2005) 3656–3657.

[8] G. Cahiez, C. Duplais, A. Moyeux, Org. Lett. 9 (2007) 3253–3254;
M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, J. Am. Chem. Soc. 126 (2004) 3686–3687.

[9] L. Ackermann, R. Born, J.H. Spatz, D. Meyer, Angew. Chem. Int. Ed. 44 (2005) 7216–7219;
A. Steffen, M.I. Sladek, T. Braun, B. Neumann, H.-G. Stammler, Organometallics 24 (2005) 4057–4064.